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To Compare the Anti-emetic Efficacy, Duration of Action, and Side Effects of Palonosetron, Ondansetron, and Granisetron for Anti-emetic Prophylaxis of Post-operative Nausea and Vomiting in Patients Undergoing Laparoscopic Abdominal Surgeries

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Abstract

Aims and Objectives: The aim of the study was to compare the anti-emetic efficacy, duration of action, and side effects of Palonosetron, Ondansetron, and Granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting. *Methodology:* We conducted a prospective, randomized, double blind study on patients undergoing laparoscopic abdominal surgeries. The total 120 patients were divided into three groups of 40 patients. Patients of group A were given injection palonosetron (0.075 mg), group B were given injection ondansetron (4 mg), and group C were given injection granisetron (1 mg), intravenously along with premedication, fifteen minutes prior to induction of general anaesthesia. We analyzed the anti-emetic efficacy, duration of action, and side effects of palonosetron, ondansetron, and granisetron. *Results:* Total incidence of nausea and vomiting was maximum in ondansetron group with total of 74 compared to 36 in granisetron and 12 in palonosetron group, considering overalapping data in all time intervals and this difference was found to be statistically major. In ondansetron group 18 patients had complete response, while complete response was higher in granisetron group (24) and highest with 28 patients in palonosetron group and this difference was statistically substantial. ($p < 0.05$). Headache and sedation was found in ondansetron group in 2 and 4 patients respectively while only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group. *Conclusion:* We conclude that palonosetron is more effective in comparison to granisetron and ondansetron in the prevention of PONV in patients undergoing elective abdominal laproscopic surgeries.

Keywords: Ondansetron; Granisetron and palonosetron' anti-emetic prophylaxis.

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Introduction

The incidence of PONV is 30–40% in a normal population with a topmost of 75–80 in some high-risk groups.[1] With the advent and usage of lesser emetogenic anaesthesia techniques and discovery of newer anti-emetogenic drugs for the post-operative nausea and vomiting prophylaxis, the

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prevalence of PONV has reduced significantly by about 50%.

Post-operative nausea and vomiting is by definition termed as nausea and vomiting which occurs within *24 hours* after surgery. Patient's clinical status, the form of surgical procedure, length of anaesthesia and surgery are few of the vital risk factors in determining of PONV. It involves three nerves and seven neurotransmitters for activation of vomiting centre, which makes the prophylaxis and treatment a tedious and complex process. Premedicating the patient with anti-emetics can reduce the rate of post-operative nausea and vomiting significantly. Various pharmacological agents, regimens, and practises were developed over a period of time, but they have restricted efficiency due to numerous side effects.[2]

Five-hydroxytryptamine subtype 3 (5-HT3) receptor antagonist are considered as one of the utmost effective anti-emetogenic agents with better safety and lesser side effects as they deprived of potential side effects of commonly used anti-emetogenic agents such as sedation, dysphoria and extra-pyramidal adverse effects.

The present study was a randomized double-blind, prospective study to compare the anti-emetic efficacy, duration of action, and side effects of intravenous palonosetron, ondansetron, and granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting in patients undergoing elective laparoscopic abdominal surgeries under general anaesthesia.

Aims and Objectives

To compare the anti-emetic efficacy, duration of action, and side effects of intravenous-palonosetron, ondansetron, and granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting in patients undergoing elective laparoscopic abdominal surgeries under general anaesthesia.

Materials and Methods

After approval by the Institutional Ethical Committee and taking written informed consent from the patient, 120 adult patients of American Society of Anesthesiologist physical status I and II, aged between *18* and *58 years* of either gender, posted for elective laparoscopic abdominal surgery under general anaesthesia from *Jan 2017* to *June 2018* in a tertiary care hospital were enrolled for current study. All the patients were undergo pre-anaesthetic assessment before enrollment.

The total 120 patients were correspondingly divided into three groups of 40 patients each according to a computer-generated random table. The study drug preparation was done by an assistant who was uninformed of our study protocol and it was done in identical 2.5 *ml* volume with normal saline to ensure blinding of the anaesthesiologist. The same was administered IV before induction of anaesthesia. The randomized process was blinded from the patients, the anaesthesiologist, and the investigators, who collected post-operative data. Patients of either sex *aged 18–55 years*, ASA I–II and posted for elective abdominal laparoscopic surgeries were included in the study. Patients with prior history of post-operative nausea and vomiting, complains of motion sickness in the past or at present. History of gastroeseophageal reflux disease, systemic hypertension, endocrine or metabolic disorders, hepatic or renal disease, cardio-pulmonary dysfunction, gastrointestinal disorders, psychiatric diseases, taken any anti-emetic *24 hours* former to the surgery and morbidly obese patients and pregnant females were excluded.

Thorough investigations include haemoglobin, complete blood count, bleeding time, clotting time, fasting blood sugar level, chest *x*-ray, urine routine and microscopic examination, serum creatinine, liver function tests.

Patients were randomly divided into three groups as described below:

Group 1	Patients receiving IV Ondansetron (4 mg)
Group 2	Patients receiving IV Granisetron (1 mg)
Group 3	Patients receiving IV Palonosetron (0.075 mg)

Informed consent of the patients were taken. All the patients were asked to fast overnight. All patients were given an anti-anxiety medication in the form of tab alprazolam 0.25 *mg* and an antacid in the form of tab ranitidine 150 *mg*, the night prior to surgery and were kept fasting for *six* to *eight hours* before the surgery. On arrival to operation-theatre, routine monitoring of heart rate, systemic arterial blood pressure, pulse oximetry (SpO_2), electrocardiogram (ECG) was initiated. After securing intravenous line, an infusion of Ringer lactate fluid was started. Patients were given premedication with intravenous midazolam (1 *mg*), fentanyl (2 µg kg^{-1}), and glycopyrrolate (0.2 *mg*) trailed by study medication according to our group allocation, fifteen minutes prior to induction of general anaesthesia.

After pre-oxygenation, induction was done with propofol (2 *mg* kg^{-1}), and tracheal intubation

was enabled with vecuronium bromide 0.08 $mgkg^{-1}$. Anaesthesia was maintained with isoflurane, N_2O (60%) in oxygen. All patients were ventilated mechanically to maintain an $EtCO_2$ between *35* and *40 mmHg*. Supplementary analgesia during the surgery was attained with fentanyl (25 µg). At the conclusion of surgery, the residual neuromuscular blockade was antagonized with suitable doses of neostigmine (0.05 $mgkg^{-1}$) and glycopyrrolate (0.01 $mgkg^{-1}$). Extubation was accomplished when the respiration was adequate and patient was able to obey simple commands.

The reference line systemic arterial blood pressure, pulse rate, and SpO_2 were recorded as a baseline parameter following premedication, after induction and then at *five min* intervals till one hour and then at every *15 min* till the end of surgery. They were watched for any hypotension, hypertension, arrhythmias, hypoxemia, and bronchial spasm. Hemodynamic variations occurring during study period were managed with volume expansion, vasopressor or atropine, if required.

Post-operatively, nausea or emetic episodes were documented by the resident doctors without the information of which group of anti-emetic drug was given to which of the patients. The side effects like headache, dizziness, and drowsiness were also noted. Post-operatively, patients were given intravenous injection of paracetamol (1 *gm*) for analgesia purpose.

Patients were asked about nausea and vomiting at *2, 4, 6,* and *12 hours* by direct questioning of the anaesthesiologist, blinded to which treatment the patient has received. Complete response was defined as no nausea, retching or vomiting and no need of rescue medication within *12 hours* in the post-operative period. At the end of each interval, an anaesthesiologist registered whether vomiting had occurred and asked the patients accordingly. Rescue medication in our study was metoclopramide 10 *mg* which was given intravenous if required.

Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software ver. 17 for analysis. Qualitative data was presented as frequency and percentages and analyzed using chi-square test. Quantitative data was presented as mean and SD and comparison of variables in more than 2 groups was done by ANOVA test. p - value < 0.05 was taken as level of significance.

Results

All the three groups were comparable as far as age, weight and NPO (nil per oral) status was concerned. The three groups were also comparable for duration of anaesthesia and surgery, pre-operative pulse rate, systolic BP and diastolic BP were concerned ($p > 0.05$) (shown as in **Table 1**).

In ondansetron group 16 patients complained of nausea, 8 patients complained of nausea in granisetron group and 5 patients of palonosetron group in *0–4 hours*. 14 patients grieved from nausea in ondansetron and 6 patients in granisetron group suffered with nausea within same time frame and 2 patients in palonosetron group suffered nausea during *4–8 hour*. 11 patients suffered from nausea in ondansetron and 5 patients in granisetron group suffered with nausea within same time frame and 0 patients in palonosetron group suffered nausea during *8–12 hour*. There was statistically substantial difference in all three groups (shown as in **Table 2**).

In ondansetron group, a total of 13 patients complained of vomiting while 7 patients complained of vomiting in granisetron group and 4 patients of palonosetron group in *0–4 hours*. 11 patients grieved from vomiting in ondansetron

Table 1: General characteristics among the three groups

General characteristics	Ondansetron	Granisetron	Palonosetron	p - value
Age	33.88 + 13.1	32.16 + 9.1	31.13 + 8.8	0.499
Weight	51.7 + 5.1	51.10 + 4.2	50.2 + 3.7	0.307
NPO	11.2 + 0.7	10.9 + 0.5	11.1 + 0.7	0.107
Duration of surgery	59.17 + 16.7	58.6 + 16.1	57.2 + 15.5	0.85
Duration of anaesthesia	93.5 + 20.2	92.6 + 19.9	91.5 + 18.8	0.92
Pulse Rate (*min*)	86.1 + 3.1	85.1 + 3.2	84.8 + 3.3	0.16
Systolic BP (*mmHg*)	114 + 5.6	113 + 5.4	112 + 5.1	0.25
Diastolic BP (*mmHg*)	82.3 + 5.1	82.1 + 4.9	80.6 + 4.3	0.22

and 6 patients in granisetron group suffered with vomiting within same time frame and 1 patients in palonosetron group suffered vomiting during *4–8 hour*. 9 patients suffered from vomiting in ondansetron and 4 patients in granisetron group suffered with vomiting within same time frame and 0 patients in palonosetron group suffered vomiting during *8–12 hour*. There was statistically noteworthy variance in all three groups (shown in **Table 2**).

Total incidence of nausea and vomiting was maximum in ondansetron group with total of 29 compared to 15 in granisetron and 9 in palonosetron group and this difference was found to be statistically momentous during *0–4 hour*, total incidence of nausea and vomiting was maximum in ondansetron group with total of 25 compared to 12 in granisetron and 3 in palonosetron group and this difference was found to be statistically noteworthy during *4–8 hour*, total incidence of nausea and vomiting was maximum in ondansetron group with total of 20 compared to 9 in granisetron and 0 in palonosetron group and this variance was found to be statistically substantial during *8–12 hour* **(**shown as in **Table 3)**.

In ondansetron group, total 18 patients had complete response, while complete response was higher in granisetron group which were 24 and highest with 28 patients in palonosetron group and this difference was statistically noteworthy (p - 0.04) **(**shown in **Table 4)**, also (shown in **Fig. 1**).

Headache and sedation was found in ondansetron group in 2 and 4 patients respectively. While only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group (shown in **Fig. 2)**.

There was very less alteration in number of patients who needed rescue medication in all the three groups. Among three groups 7, 5 and 2 patients required rescue medication in ondansetron, granisetron and palonosetron group respectively.

Table 2: Number of patients with post-operative nausea (PON) and post-operative vomiting in different groups in study population.

	Time	Ondansetron	Granisetron	Palonosetron	p - value
Post-perative nausea	*0–4 hour*	16 (25%)	8 (20%)	5 (12.5%)	0.04
	4–8 hour	14 (15%)	6 (10%)	2 (10%)	0.002
	8–12 hour	11 (12.5%)	5 (5%)	0 (7.5%)	0.001
	Total	40 (100%)	40 (100%)	40 (100%)	
Post-operative vomiting	*0–4 hour*	13 (25%)	7 (20%)	4 (12.5%)	0.03
	4–8 hour	11 (15%)	6 (10%)	1 (10%)	0.007
	8–12 hour	9 (12.5%)	4 (5%)	0 (7.5%)	0.005
	Total	40 (100%)	40 (100%)	40 (100%)	

Table 3: Number of patients with total post-operative nausea and vomiting (TPNV) in different groups in study population.

Time	Ondansetron	Granisetron	Palonosetron	p - value
0–4 hour	29 (25%)	15 (20%)	9 (12.5%)	0.001
4–8 hour	25 (15%)	12 (10%)	3 (10%)	0.001
8–12 hour	20 (12.5%)	9 (5%)	0 (7.5%)	0.001
Total	40 (100%)	40 (100%)	40 (100%)	

Table 4: Number of patients with complete response (CR) *i.e.*, free from both nausea and vomiting throughout intra-operative and post-operative period.

Groups	TNV	CR	Total
Ondansetron	22 (55%)	18 (45%)	40 (100%)
Granisetron	16 (41%)	24 (59%)	40 (100%)
Palonosetron	12 (31%)	28 (69%)	40 (100%)

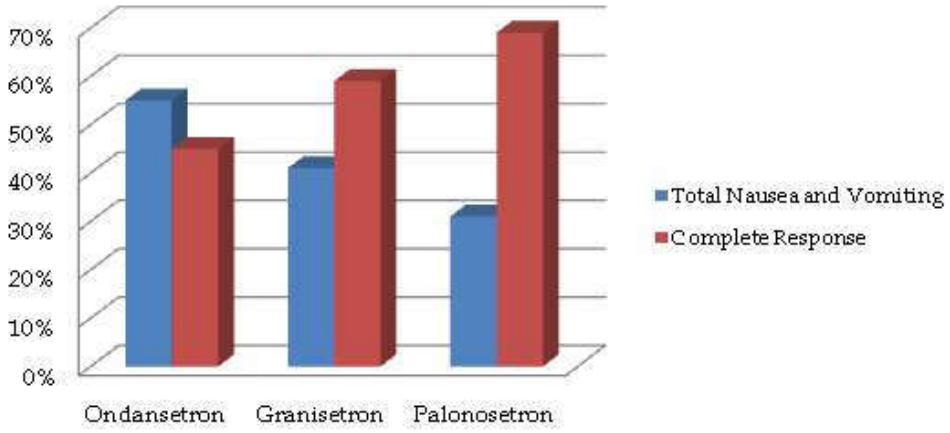

Fig. 1: Number of patients with complete response (CR) *i.e.*, free from both nausea and vomiting throughout intra-operative and post-operative period.

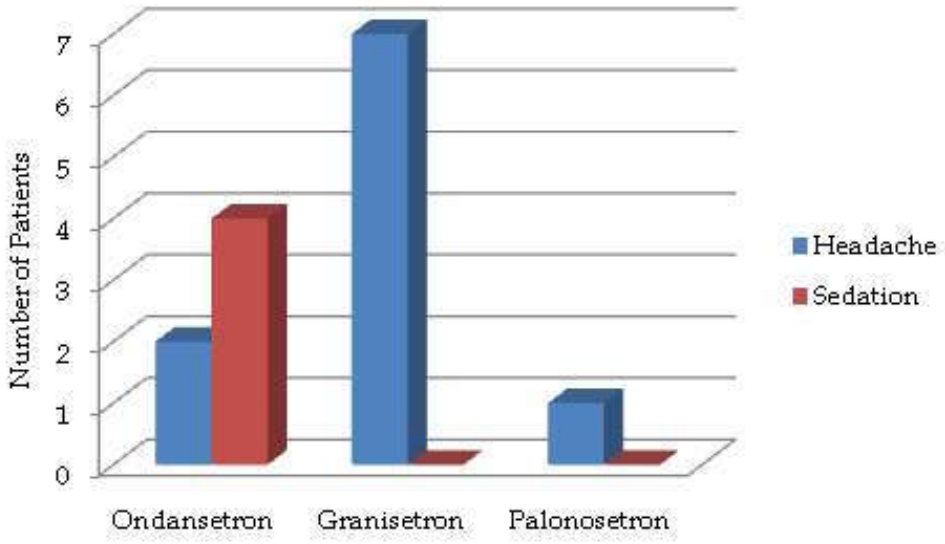

Fig. 2: Side effects experienced by number of patients in different groups

Discussion

The aetiology of the PONV is intricate and multifactorial. Pre-operative anxiety, positive pressure ventilation, inhalational anaesthetic agents, and nitrous oxide increase the jeopardy of PONV. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT3 receptors on the chemoreceptor trigger zone (CTZ). PONV is more common in younger age group and in obese patients.[3,4] Apfel *et al.*, 2004 considered laparoscopic surgery, female gender, non-smokers, a history of PONV, motion sickness, and post-operative opioid therapy as important independent causal factors for PONV.[5]

Anti-emetic drugs incline to have more noticeable action at one or two receptors while 5-HT3 receptor antagonists are highly specific and selective for its action against nausea and vomiting by binding to the serotonin 5-HT3 receptor in the chemoreceptor trigger zone (CTZ) and at vagal efferent in the gastrointestinal tracts.[6,7]

In the current study, as per the demographic data obtained the mean age of study population in ondansetron group was 33.88 + 13.1, granisetron group was 32.16 + 9.1 and in palonosetron group was 31.13 + 8.8 and there was no noteworthy variance between all groups. Obesity is usually seen to be associated with increased incidence of PONV. In our study the mean weight was 53.7 + 5.1 *kg*, 51.10 + 4.2 *kg*, 49.2 + 3.7 *kg* in ondansetron, granisetron and in palonosetron group and the episodes of PONV was non-pointedly higher in ondansetron, granisetron as compared to palonosetron.

The occurrence of PONV may be linked with many features including: Age and gender (female gender and younger age than adulthood increase the risk of PONV); previous history of motion sickness or PONV; smoking status (smoking decreases the risk of PONV); post-operative opioid use; nature and length of surgery; anaesthesia and ambulation.[8–10] In the current study, the mean duration of anesthesia and surgery were almost comparable with no substantial statistical variance in all three groups. In the study, directed by Sukhminderjit Singh Bajwa *et al.,* 2011, the mean duration of surgery in ondansetron group was 27.86 ± 4.68 and in palonosetron group was 29.24 ± 3.88 and the mean duration of anaesthesia in ondansetron group was 36.42 ± 2.58 and in palonosetron group was 38.26 ± 2.96.[7] In the current study, pre-operatively the mean pulse rate, SBP, DBP in all the groups showed no substantial alteration. This findings is in arrangement with the study directed by Neha Sharma *et al.,* there was no substantial changes in systolic and diastolic pressure among the groups of studied patients.[11]

In the current study, in ondansetron group, a total of 16 patients grieved of nausea, 8 patients complained of nausea in granisetron group and 5 patients of palonosetron group in *0–4 hours*. 14 patients grieved from nausea in ondansetron and 6 patients in granisetron group agonised with nausea within same time frame and 2 patients in palonosetron group agonized nausea during *4–8 hour*. 11 patients grieved from nausea in ondansetron and 5 patients in granisetron group agonized with nausea within same time frame and 0 patients in palonosetron group suffered nausea during *8–12 hour*. There was statistically noteworthy difference in all three groups. This findings is in contract with the study shown by Neha Sharma *et al.,* nausea was observed in 18 patients, 10 patients, 3 patients of ondansetron, granisetron and palonosetron group respectively and this difference was statistically momentous.[11]

Similarly in the study conducted by Kumkum Gupta *et al.,* 2014, 30% patients grieved from nausea in ondansetron group, 5% patients in palonosetron group within *0–4 hrs*. There was statistically substantial modification in all two groups.[12]

In the current study, in ondansetron group, a total of 13 patients complained of vomiting, 7 patients complained of vomiting in granisetron group and 4 patients of palonosetron group in *0–4 hours*. 11 patients grieved from vomiting in ondansetron and 6 patients in granisetron group grieved with vomiting within same time frame and 1 patients in palonosetron group agonized vomiting during *4–8 hour*. 9 patients suffered from vomiting in ondansetron and 4 patients in granisetron group agonized with vomiting within same time frame and 0 patients in palonosetron group grieved vomiting during *8–12 hour*. There was statistically noteworthy variance in all three groups. This findings is in arrangement with the study shown by Neha Sharma *et al.,* nausea was detected in 18 patients, 10 patients, 3 patients of ondansetron, granisetron and palonosetron group respectively and this difference was statistically substantial.[11] Similarly in the study, directed by Kumkum Gupta *et al.,* 2014, 25% patients agonized from vomiting in ondansetron group, 5% patients in palonosetron group within *0–4 hrs*. There was statistically momentous variance in all two groups.[12] Comparable findings were observed in the study led by Park *et al.,* 2011 in which palonosetron was superior to ondansetron for control of post-operative nausea and vomiting.[13]

In the current study, total occurrence of nausea and vomiting was maximum in ondansetron group with total of 29 compared to 15 in granisetron and 9 in palonosetron group and this difference was found to be statistically noteworthy during *0–2 hour*, total occurrence of nausea and vomiting was extreme in ondansetron group with total of 25 compared to 12 in granisetron and 3 in palonosetron group and this variance was found to be statistically momentous during *4–8 hour*. Total occurrence of nausea and vomiting was all-out in ondansetron group with total of 20 compared to 9 in granisetron and 0 in palonosetron group and this transformation was found to be statistically important during *8–12 hour*.

In the current study, in ondansetron group 18 patients had complete response, while complete response was higher in granisetron group (24) and highest with 28 patients in palonosetron group and this difference was statistically significant. ($p < 0.05$). This findings is in arrangement with the study directed by Neha Sharma *et al.,* palonosetron was linked with greater patients gratification than granisetron and ondansetron 69%, 59% and 45% of patients, respectively ($p = 0.032$) and this modification was found to be statistically unimportant.[11] Palonosteron was further more effective at dropping PONV rates than granisetron and ondansetron. This could reflect the high receptor affinity of palonosetron for 5-HT3, with a low affinity established for other receptors including 5-HT1A, 5-HT1D, 5-HT2A and 5-HT2C, and the longer duration of action.[14,15] Palonosetron was superior to ondansetron in reducing overall PONV.[16]

In the current study, headache and sedation was observed in ondansetron group in 2 and 4 patients respectively. While only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group. Likewise in the study directed by Park *et al.*, 2011 in which headache was observed in 8.9% and 6.7% while dizziness was present in 11.1% and 11.1% of ondansetron and palonosetron group correspondingly (though statistically not noteworthy).[13]

In the current study, there was very less variance in number of patients who required rescue medication in all the three groups. Metoclopramide was used as our rescue medication. It is a "prokinetic drug" that stimulates the muscles of GIT counting muscles of lower esophageal sphincter, stomach, and small intestine by networking with receptors for acetylcholine and dopamine on gastrointestinal muscles and nerves. It reduced the reflux of gastric acid by strengthening the muscles of lower esophageal sphincter. Amongst three groups 7, 5 and 2 patients needed rescue medication in ondansetron,granisetron and palonosetron group individually. This findings is in covenant with the study shown by Neha Sharma *et al.*, in which need for additional rescue anti-emetic medication was required in 13.3% of patients with palonosetron, 30.0% with granisetron and 46.7% with ondansetron (p = 0.02) in this study.[11] Likewise in the study shown by Park *et al.*, in which rescue medication in was used in 15.6% and 17.8% of palonosetron and ondensetron group correspondingly though statistically not important.[13]

Both palonosetron and granisetron are 5-HT3 antagonists; however, palonosetron has a superior binding affinity and a lengthier biological half-life when matched to older 5-HT3 antagonists such as granisetron and interrelates with 5-HT3 receptors in an allosteric, positively co-operative manner at other sites, leading to long-lasting effects on receptor ligand binding and functional responses.[17,18] This could be the reason for the improved control of late onset PONV (nausea 2–48 h, p = 0.037) in the palonosetron group compared to the granisetron group even though the findings of the two drugs were almost analogous in early onset PONV.

Conclusion

Palonosetron is more effective in comparison to granisetron and ondansetron in the prevention of post-operative nausea and vomiting in patients undergoing elective abdominal laproscopic surgeries. Ondansetron, granisetron and palonosetron were comparable in the prevention of early PONV, but palonosetron was much more operational in the prevention of delayed PONV according to our study.

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Study on Granisetron, Ondansetron and Palonosetron to Prevent Post-operative Nausea and Vomiting after Laparoscopic Surgeries

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Abstract

Introduction: Post-operative nausea and vomiting (POVN) is a common condition and causes much discomfort to the patient. It is not only unpleasant but also can have serious consequences like that of gastric content aspiration, rupture of esophagus, opening up of wounds, subcutaneous emphysema, or pneumothorax. *Aim of the Study:* To compare the anti-emetic effects of intravenous granisetron, ondansetron and palonosetron for prophylaxis of post-operative nausea and vomiting after laparoscopic surgeries under general anesthesia. *Materials and Methods:* This was a prospective, randomized, double-blinded, comparative study. A total of 75 patients were divided randomly into three groups each having 25 subjects. Group-A received ondansetron 8 mg, Group-B received Granisetron 2.5 mg and Group-C received Palonosetron 0.75 ug. Both male and female patients, ASA I–II with age ranging from 18–65 years and who underwent elective laparoscopic surgeries under general anesthesia were selected.The incidence of post-operative; nausea, retching and vomiting were studied. *Observations and Results:* Age, gender and weight were insignificant in all the 3 Groups. Groups-A/C was found to be statistically significant ($p < 0.05$) in 24–48 and also 12–24 hours. Retchingwas significantly less in Group-C when compared to other two groups. Incidence of vomiting was significantly less in Group-C when compared to Group-A and B. The p-value between Group–A and C was found to be statistically significant ($p < 0.05$) in 24–48 hours. *Conclusion:* Prophylactic therapy with palonosetron is more effective than prophylactic therapy with ondansetron and granisetron for the long-term prevention of PONV after laparoscopic surgery.

Keywords: Granisetron; Ondansetron; Palonosetron; PONV; Laparoscopic surgeries.

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Introduction

Pain and vomiting/emesis are common after anesthesia and surgery. They cause anxiety and distress to the patients. Post-operative nausea, retching and vomiting individually or in combination are identified as 'sickness' and each symptom is considered a separate entity. Post-operative nausea and vomiting (PONV) has been characterized as big little problem and is

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a frequent complication for both inpatients and outpatients undergoing virtually all types of surgical procedures. Earlier, in the 'Ether Era' the incidence of PONV was high and was about 75% to 80%. In the present scenario, it is comparatively less and is about 22% to 30% in adult patients.

According to the literature, incidence of PONV ranges from 25% to 55% in inpatients who have undergone surgery and 8% to 47% in outpatients.[1] It was observed that patients are concerned more about post-operative nausea and vomiting which can be quite distressing. PONV when severe and/or prolonged, can lead to wound dehiscence, bleeding from operative sites, venous hypertension, tears or rupture in the esophagus, if severe it may cause fracture in the ribs, herniation of stomach and also muscular fatigue. Persistent PONV is especially dangerous in post-operative neurosurgical cases where it can lead to raised intracranial pressure and also predispose to pulmonary aspiration. In the paediatric population, persistent vomiting can cause detrimental dehydration and electrolyte imbalance.[2]

Addressing the complications of PONV results in increased costto the patient, longer recovery time, extended bed occupancy in the hospital, added attention and time constraints for the nurses and physicians and also inconvenience to the family as a whole. Patients undergoing laparoscopic surgeries are more likely to encounter PONV. In laparascopic surgeries due to the presence of pneumo-peritoneum, the mechano receptors in the gut are stimulated much more, thereby leading to PONV.

The commonly used anti-emetic drugs like anti-histaminic, anti-cholinergics and dopamine receptor antagonists have clinically significant side effects, such as sedation, dry mouth, dysphoria and extra pyramidal symptoms. 5HT3 receptor antagonists are potent anti- emetics.[3] The present study was done to compare anti-emetic effects of intravenously administered granisetron, ondansetron and palonosetron for prophylactic PONV in patients undergoing laparoscopic surgeries under general anesthesia.

Materials and Methods

This was a prospective, randomized, double-blinded, comparative study approved by the institution ethical committee. Informed consent was obtained from all the patients. The study group consisted of 75 ASA I–II male and female patients with age ranging from *18* to *65 years*. All the patients were posted for elective laparoscopic surgeries under general anesthesia and were randomly allotted to the groups, each containing twenty-five patients.

Exclusion Criteria

Patients with known gastrointestinal disease, smokers, patients with history of motion sickness, post-operative nausea and vomiting, pregnant women and menstruating women were excluded. Also those who had taken anti-emetic medication within past *24 hours* were excluded.

Using computer generated randomization technique these patients were divided into three groups each containing 25 individuals. Group-A received ondansetron 8 *mg*, Group-B received Granisetron 2.5 *mg* and Group-C received Palonosetron 0.75 *ug* along with premedication, immediately before induction of general anesthesia. Normal saline was added to bring the total injectable volume to 2.5 *ml* in each group. Two theatre assistants were used for group allotment of the patients and to prepare the study drugs. However, both were unaware of the study protocol and were uninvolved in any further evaluation of the patients.

All patients were kept nil orally after midnight. In the operation room, routine monitoring (ECG, pulse oximetry, NIBP) were attached and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO_2) were noted. An intravenous line was secured. All patients were premediated with inj. Glycopyrrolate 0.2 *mg*, inj. Midazolam 0.03 *mg/kg*, inj. Tramadol 2 *mg/kg* intravenously.

After pre-oxygenation for *3 minutes*, induction of anesthesia was done with inj. Thiopental 5 *mg/kg*. Patients were intubated with inj. Succinyl choline 2 *mg/kg* with appropriate size endotracheal tube. Anesthesia was maintained with 33% oxygen, nitrous oxide 67%. Muscle relaxation was maintained with inj. Vecuronium bromide and supplemented with Isoflurane. Mechanical ventilation was used to keep EtCO2 between 32–35 *mm Hg*. The stomach contents were emptied by a nasogastric tube. For the laparoscopic procedure, the peritoneal cavity was insufflated with carbondioxide. Intra-abdominal pressure was kept < 14 *mm Hg*. At the end of surgical procedure, residual neuromuscular block was adequately reversed using intravenous glycopyrrolate 1 *ug/kg* and neostigmine 0.05 *mg/kg* and then extubation was done. Before tracheal extubation, post-operative analgesia, injection diclofenac sodium-75 *mg* intramuscular was given

when pain score was > 4 Visual Analog Score (VAS). Resident doctors who were unaware of the study drug observed all the patients post-operatively and noted the findings. Patients were transferred to post-anesthesia care unit and vitals were monitored. All episodes of PONV (nausea, retching and vomiting) were recorded at intervals of 6, 12, 24 and *48 hours* in post-operative ward.

Nausea was defined as an unpleasant sensation with an urge to vomit. Retching was defined as the labored, spastic, rhythmic contraction of the respiratory muscles without the actual emesis. Complete response (free from emesis) was defined as no PONV and no need for any rescue medication. Injection metoclopramide 10 *mg* IV was given as rescue medication if they vomited more than twice. At the end of each time interval it was recorded, if the patient had vomiting or any sensation of nausea or retching.

The result was scored as nausea-1, retching-2, and vomiting-3 and statistical analysis was performed with the SPSS 17.0 for Windows Software. The normally distributed data were compared using Student's *t*-test. For comparison of skewed data, Mann-Whitney *u*-test was applied. Qualitative or categorical variables were described as frequencies and compared with Chi-square or Fisher's exact test whichever was applicable. *p* - values were corrected by the Bonferroni method and $p < 0.05$ was considered statistically significant.

Results

A total of 75 ASA grade I–II male and female patients, aged *18–65 years* were studied for PONV following elective laparoscopic surgeries under general anesthesia, (**Tables 1–7** and **Fig. 1**).

Table 1: Demographic data in study

Group	Age (in years)	Weight	Female	Male
A	28.72 ± 9.91	51.2 ± 5.5	18	7
B	30.5 ± 12.8	50.64 ± 5.39	17	8
C	30.1 ± 8.99	50.6 ± 5.28	18	7

All the groups are similar with regard to age, weight and gender.

Table 2: Incidence of nausea among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	3	3	7	11
B	1	2	4	6
C	1	1	1	3

The incidence of nausea was significantly less in Group-C as compared to Group-A and Group-B.

Table 3: Correlation of nausea in three groups in first *48 hours*

Group	Interval	*p* - value
A/C	*0–6 hrs*	0.60
	6–12 hrs	0.60
	12–24 hrs	0.04*
	24–48 hrs	0.02*
A/B	*0–6 hrs*	0.60
	6–12 hrs	1.00
	12–24 hrs	0.49
	24–48 hrs	0.23
B/C	*0-6 hrs.*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.34
	24–48 hrs	0.46

The *p* – value between Groups-A and C was found to be statistically significant ($p < 0.05$) in *24–48 hours* and also *12–24 hours*. The *p* - value was statistically insignificant ($p > 0.05$) in all other cases.

Table 4: Incidence of retching among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	1	2	3	5
B	0	1	2	3
C	0	1	1	2

Table 5: Correlation of retching among the three groups in first *48 hours*

Group	Interval	*p* - value
A/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.60
	24–48 hrs	0.42
A/B	*0–6 hrs*	1.0
	6–12 hrs.	1.0
	12–24 hrs	1.0
	24–48 hrs	0.70
B/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	1.0
	24–48 hrs	1.0

The incidence of retching was significantly less in Group-C as compared to Group-A and Group-B. The *p* - values among all the groups were statisticallyinsignificant ($p > 0.05$).

Table 6: Incidence of vomiting among the three groups in first *48 hours*

Group	*0–6 hrs*	*6–12 hrs*	*12–24 hrs*	*24–48 hrs*
A	2	3	5	11
B	1	2	5	6
C	0	1	2	3

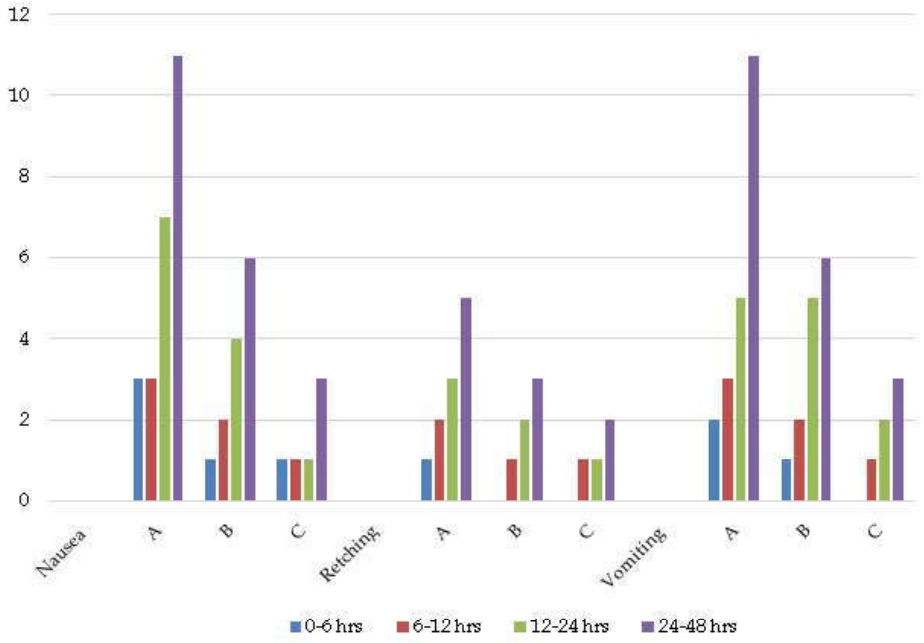

Fig. 1: Incidence of nausea, retching and vomiting in the three groups

(Pl. use **N-dash in Hrs Range)

Table 7: Correlation of vomiting among the three groups in first *48 hours*

Group	Interval	*p* - value
A/C	*0–6 hrs*	0.48
	6–12 hrs	0.60
	12–24 hrs	0.412
	24–48 hrs	0.02*
A/B	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	1.0
	24–48 hrs	0.13
B/C	*0–6 hrs*	1.0
	6–12 hrs	1.0
	12–24 hrs	0.417
	24–48 hrs	0.70

Incidence of vomiting was significantly less in Group-C when compared to Group A and B. The *p* - value between Group-A and C was statistically significant ($p < 0.05$) in 24–48 hours. The *p* - value was not statistically significant ($p > 0.05$) in all other cases.

Incidence was less in group C (Palonosetron) when compared to group A and B.

Discussion

Nausea and vomiting following general anesthesia are a distressing problem for the patients and are frequently listed among the most important pre-operative concerns apart from pain. With changing trends of increased outpatient office based medical/surgical environment, more emphasis is focused on the "the big little problem" of PONV following general anesthesia.

In spite of much advancement in the management of PONV with the invention of new drugs, multimodal approaches of management like administering multimodal approaches of management like administering multiple different anti-emetic medications, less emetogenic-anesthetic techniques, adequate intravenous hydration, adequate pain control etc., the incidence of post-operative nausea and vomiting remains still high, ranging from 25%–55% following inpatient surgery and 8%–47% following outpatient surgery.[4]

An effective anti-emetic that could be used to treat nausea and vomiting without extending recovery time and that remain effective for *48 hours* following treatment would be significant asset to the anesthesiologist's armamentarium, especially in settings like office based anesthesia where the patients is admitted for day care surgery and is discharged on the same day. Drugs acting for longer duration also have an advantage in surgeries where the incidence of post-operative nausea and vomiting is very high like laparoscopic surgery, middle ear surgery, tonsillectomy, laparotomy, strabismus surgery, orchidopexy, etc.[4,5]

Unfortunately, commonly used anti-emetic medications like antihistamines, anticholinergics, gastroprokinetic, butyrophenones cause undesirable side effects like sedation, dysphoria, restlessness and extrapyramidal symptoms. To overcome this later serotonin antagonists like ondansetron, tropisetron, dolasetron, granisetron and palonosetron were introduced for treatment of nausea and vomiting. They were primarily used in treating chemotherapy induced vomiting with minimal and clinically acceptable side effects. The most distressing and intolerable emesis induced by anti-malignant medication is better controlled with these 5HT antagonists and they proved to have a promising role in the field of oncology. Abundant research in oncology demonstrates the efficacy of these drugs. However, there were many reports in the literature about their role in prevention of post-operative nausea and vomiting.

Post-operative period has variable incidence of nausea and vomiting. PONV depends on the duration of surgery, the type of anesthetic agents used (dose, inhalational drugs, opioids), smoking habits, etc. Vomiting reflexes are initiated by 5-HT receptor stimulation. The vagus nerve terminals bear these receptors and they are also present centrally on the chemoreceptor trigger zone (CTZ) of the area postrema. Anesthetic agents initiate the vomiting reflex as they stimulate the central 5HT receptors on the CTZ. These agents also release serotonin from the enterochromaffin cells of the small intestine and cause stimulation of 5-HT receptors on afferent fibers of vagus nerve.[6]

The incidence of PONV after laparoscopic surgery is high (40–75%). The etiology of PONV after laparoscopic surgery is complex and is dependent on patient age, body weight, history of previous PONV, the type of surgical procedure and technique of administration of anesthesia. In the present study, however, all the groups were comparable with respect to patient demographics, anesthesia and analgesics used post-operatively. Therefore, the difference in a complete response (on PONV, no rescue medication) between the groups can be attributed to the study drug.

Emesis related to cancer chemotherapy responds well to Granisetron. The exact mechanism of action of granisetronis unclear, but it is proposed that granisertron may act on sites containing 5-HT receptors with demonstrated anti-emetic effects. Palonosetron is a unique 5-HT receptor antagonist and is widely used for the prevention of chemotherapy related nausea and vomiting. It has a greater binding affinity and longer biological half-life than older 5-HT receptor antagonists. The proposed mechanism of palonosetronis that it functions via the area postrema which contains many 5-HT receptors. Therefore, granisetron and palonosetron may have similar mechanisms to exert anti-emetic effect in preventing PONV.[7]

For chemotherapy related nausea and vomiting the effective dose of granisetron is 40–80 *ug*. A dose of granisetron 2.5 *mg* (approximately 45 *ug/kg*) was used in this study as the effective dose range is (40–80). However, the dose of palnonosetron for the prevention of PONV is not established but was extrapolated from the dose used in clinical trials. Kovac LA and colleagues demonstrated that palonosetron 75 *ug* is the more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25 *ug* and 50 *ug*.

In our study, we compared the anti-emetic efficiency of ondansetron, granisetron and palonosetron post-operatively for laparoscopic surgeries in first *48 hours*. Our study demonstrates that in the first *12 hours* anti-emetic efficiency of all three drugs (ondansetron, granisetron and palonosetron) is similar and the difference is statistically not significant.

Palonosetronis more effective than ondansetron and granisetron for getting complete response (no PONV, no rescue medication required) for *24–48 hours* and the p - value < 0.05) is statistically significant between ondansetron and palonosetron groups in *24 to 48 hours*.

This suggests that palonosetron has longer lasting anti-emetic effect as compared to the other two drugs. The variable effectiveness of these drugs could be related to their half-lives (ondansetron *3–4 hours*, granistron *8–9 hours*, versus palonosetron *40 hours*.) It could also be due to the binding affinities of 5-HT receptor antagonists as palonosetron interacts with 5-HT receptors in an allosteric, positive manner at sites different from those of ondansetron and granisetron.

Bhattacharya *et al*.[8] reported that granisetron is superior to ondansetron for prevention of PONV. They observed that incidence of PONV was less with granisetron when compared to ondansetron within first *6 hours* post-operatively in patients undergoing day care gynecological laparoscopy. These findings are in agreement with our study where incidence of PONV was less with ondansetron and granisetron in first *6 hours*.

Bhattacharjee *et al*.[5] reported that the incidence of PONV was less with palonosetron when compared with granisetron within *24–48 hours* in patients

undergoing laparoscopic cholecystectomy. These findings are similar to our observations.

Mehta *et al.*[9] compared ondansetron and granisetron for prevention of PONV following elective caesarean section and concluded that both the drugs had significantly reduced PONV. Our study correlates well with their study in early prevention of PONV with ondansetron and granisetron.

Tahir *et al.*[10] did study on palonosetron in the prevention and treatment of PONV and found that palonosetron is effective in preventing delayed period of PONV up to *24–72 hours*. Our study concurs with their study in the prevention of late period of PONV (*24–48 hours*) with palonosetron.

Sarbari *et al.*[11] studied the efficacy of Ramosetron, Palonosetron and Ondansetron for preventing post operative nausea and vomiting in female patients undergoing laparoscopic cholecystectomy, the incidence of post-operative nausea and vomiting was 34.5%, 62.1% and 65.5% respectively, representing a significant overall difference ($p = 0.034$) as well as between Ramosetron and Ondansetron ($p = 0.035$). Ramosetron was labeled to be a better prophylactic anti-emetic than Palonosetron or Ondansetron in female patients under general anesthesia.

We did not include a control group receiving placebo in our study. Aspinall and Goodman[12] have suggested that if active drugs are available then placebo controlled trials should not be done as it would be unethical because PONV cause much anxiety and distress to the patients.

Conclusion

We conclude that anti-emetic prophylaxis with 5-hydroxytryptamine subtype 3 (5-HT3) antagonists provides clinically effective prevention of post-operative nausea and vomiting. These drugs have statistically significant difference in their efficacy and duration of action. Palonosetron is a better drug for anti-emetic prophylaxis of PONV in patients undergoing laparoscopic surgery under general anesthesia as compared to ondansetron and granisetron as it has prolonged duration and minimal side effects. Prophylactic therapy with palonosetron is more effective than prophylactic therapy with ondansetron and granisetron for the long-term prevention of PONV after laparoscopic surgery.

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Original Research Article

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Comparative Evaluation of Nalbuphine and Tramadol as an Adjuvant to 0.5% Bupivacaine in Supraclavicular Brachial Plexus Block

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Abstract

Background: Brachial plexus block is a reliable, regional anesthetic technique for upper arm surgeries. Opioid agonist-antagonists are used as adjuvant to enhance the analgesia of bupivacaine. The present study was aimed to compare the analgesic efficacy and safety of nalbuphine and tramadol as an adjuvant to 0.5% bupivacaine for brachial plexus block. *Materials and Methods:* Thirty adult patients of ASA I and II of both genders were randomized into two Groups of fifteen patients, Group BT receive 28 ml of 0.5% bupivacaine with 2 ml of tramadol and Group BN receive 28 ml of 0.5% bupivacaine with 2 ml of nalbuphine 20 mg for supraclavicular brachial plexus block. Patients were observed for onset and duration of sensory and motor block with duration of pain relief as primary end points while occurrence of any adverse effect due to technique or nalbuphine was noted as secondary outcome. *Results:* In Group BN, there was a statistically significant shorter time to onset of sensory blockade (10.46 ± 1.5 min vs 13.66 ± 2.5 min, $p < 0.001$), shorter onset time to achieve motor block (14.4 ± 2.5 min vs. 18.46 ± 3.5 min, $p < 0.001$), longer duration of motor block (291.4 min vs 363.07 min, $p < 0.001$), and prolonged analgesia (456 min vs 409.13 min, $p = 0.003$). No significant side effects were seen in any of the groups. *Conclusion:* Addition of nalbuphine to 0.5% bupivacaine in supraclavicular brachial plexus block significantly hastens the onset, and prolongs the duration of sensorimotor blockade and analgesia when compared with tramadol as an additive. Both the drugs were comparable in terms of safety.

Keywords: Brachial plexus block; Bupivacaine; Nalbuphine; Tramadol; Additive.

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Introduction

The supraclavicular block is often called the "spinal anesthesia of the upper extremity" because of its ubiquitous application for upper extremity surgery. It is a reliable, alternative to general anesthesia for certain group of patients as it is devoid of undesired effects of general anesthesia and stress of laryngoscopy. The post-operative period is also free from pain, nausea, vomiting, and respiratory depression. The supraclavicular approach is chosen for brachial plexus block as here it is enclosed in a fascial sheath that extends from neck to the axilla.[1] The success of brachial plexus block relies on nerve localization, needle placement, and deposition of local anesthetic solution at right place by a single injection of local anesthetic.[1] Nerve stimulatorare

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better than blind technique as they not only increase the accuracy but also prevent several complication that may arise due to blind technique. It also minimizes the local anesthetic volume, thereby reducing the incidences of their systemic toxicity.[2,3] Bupivacaine relieves pain by blocking the transmission of pain signals to the dorsal horn, but it has definite risks of systemic toxicity, especially with brachial plexus block. Various adjuvants like opioids, clonidine, dexmeditomedine are added in peripheral nerve blocks to increase speed of onset, duration of action, improve quality of the block and to reduce toxicity of local anesthetics.[4] However, they are associated with side effects like heavy sedation and respiratory depression. Therefore, there is always look out for drugs with minimal side effects. Opioids have an anti-nociceptive effect at the central or spinal cord levels. Stimulation of opioid receptors on neurons of central nervous systems leads to the inhibition of neuronal serotonin uptake which leads to augmentation of spinal inhibitory pain pathways; however, it is still unclear whether functional opioid receptors exist in peripheral tissue.[5] Many opioids such as tramadol and fentanyl have been added as adjuvants to local anesthetics by different routes, including brachial plexus block, to enhance the analgesic efficacy. Effects of opioids are either by their action on opioid receptors or by systemic absorption. Tramadol is an analgesic with μ mixed opioid and non-opioid activity. It inhibits the reuptake of norepinephrine (NE) and serotonin from the nerve endings and potentiates the effects of local anesthetics when mixed together in peripheral regional nerve block. It has less respiratory depressant effect due to weak μ receptor affinity.[6]

Nalbuphine hydrochloride, a potent analgesic,[7] acts as a Kappa agonist and partial mu antagonist.[7,8,10] Its affinity to κ-opioid receptors results in sedation, analgesia, and cardiovascular stability with minimal respiratory depression.[7,10]

It may potentiate local anesthetic action through central opioid receptor-mediated analgesia by peripheral uptake of nalbuphine to systemic circulation. It is widely studied as an adjuvant to local anesthetics in central neuraxial techniques by epidural, caudal, and intrathecal routes.[11] However, after research in literature, we did not find much published data studying the effect of nalbuphine as an adjuvant to local anesthetics in peripheral nerve blocks however, we are commonly using tramadol as an adjuvant to local anesthetic in our institute.

Hence, the present study was undertaken to compare the clinical efficacy and safety of tramadol versus nalbuphine as an adjuvant to 0.5% bupivacaine for supraclavicular brachial plexus block. The primary aim of this study was to compare tramadol versus nalbuphine as an adjuvant to 0.5% bupivacaine in supraclavicular brachial plexus blocks in terms of onset of block, duration of sensory and motor blockade and post-operative duration of analgesia and secondary aim is to compare safety of the two drugs in the form of side effect profile.

Materials and Methods

After approval of the Institutional Ethics Committee and obtaining written informed consent from each patient, thirty patients of American Society of Anesthesiologists (ASA) physical status I to II of both gender, aged *18–60 years*, scheduled for elective elbow, forearm and hand surgeries in orthopedic operation theatres, were enrolled for this prospective, randomized comparative control study.

Patients with clinically significant coagulopathy, infection at the injection site, allergy to local anesthetics, pre-existing neuromuscular diseases, severe cardiovascular or pulmonary disease, renal or hepatic disorder, refusal to technique, unco-operative or failure of block were excluded from the study. Patients on any opioids or any sedative medications in the week prior to the surgery were also excluded from the study. Visual analog scale (VAS) was explained to all patients where 0 corresponds to no pain and 10 indicates the worst unbearable pain.

Patients were randomized according to computer-generated random number table into two equal groups of fi fteen patients each, Group BT (Bupivacaine with tramadol) and Group BN (Bupivacaine with nalbuphine). Patients of Group BT received 28 ml of 0.5% bupivacaine with 2 ml (100 mg) of tramadol and patients of Group BN received 28 ml of 0.5% bupivacaine with 2 ml (20 mg) of nalbuphine for brachial plexus blockade by supraclavicular approach.

The study drug solutions were in similar volume of 30 ml, to maintain the blindness of study and were prepared by an anesthetist who was not involved for data collection of the patients. The anesthetist performing the block was also blinded to the study groups, and all observations were done by the same investigator.

All patients were admitted before the day of surgery, and fasting of *8 hours* was ensured. On arrival in the operation theatre, intravenous

access was established and lactated ringer lactate solution was infused at the rate of *6–8 ml/kg* and monitors for non-invasive blood pressure, heart rate, electrocardiogram (ECG), and pulse oximetry (SpO_2) were commenced to monitor the peri-operative vital parameters of patients. Patients lie down supine with head turned *45°* to the contralateral side with adduction of ipsilateral arm. A small bolster was placed between shoulder blades to make the plexus taut. The supraclavicular brachial plexus block was performed using a Vygon nerve stimulator with *22 g, 5 cm* insulated needle for precise location of brachial plexus. Under all aseptic precautions, a skin wheal was raised in the supraclavicular region, *1 cm* above the medial two third and the lateral one third of the clavicle. Subclavian artery is usually palpable on this site. Nerve stimulator frequency was set at *2 Hz* and intensity of stimulating current was initially set to deliver *1 mA* for *0.1 ms*. Insulated needle was inserted through the skin wheal in a posterior, caudal and medial direction until a distal motor response was elicited. As the nerve was approached, movement of the wrist or fingers were identified and the current was gradually reduced to *0.5 mA*. Position of needle was considered acceptable when an output current *0.5 mA* elicited a distal motor response. At this point after negative aspiration for blood, a mixture of local anesthetic and adjuvant as per the group allotted was given. All patients were given supplemental oxygen using ventimask. The onset of sensory block was assessed by pinprick method. The onset time of sensory block was the time from completion of the injection to first loss of pinprick sensation.

Motor weakness was assessed by hand grip and movement at the elbow, wrist and fingers, using a modified Bromage scale (Grade 0 - normal motor function, able to raise the extended arm to *90°*; Grade 1 - able to flex the elbow and move the fingers but unable to raise the extended arm; Grade 2 - unable to flex the elbow but able to move the fingers; Grade 3 - complete motor block). The onset time of motor block was the time from completion of the injection to reduction of muscle force to Grade 2. Motor block was also assessed by thumb abduction (radial nerve), thumb adduction (ulnar nerve), and thumb opposition (median nerve). Duration of motor block was taken from onset of motor block to complete recovery of full muscle power and was determined by asking the patients to note the time when they could first move their fingers of blocked limb. Patients were assessed for onset of sensory and motor blockade at every *2 min* interval till desired surgical anesthesia achieved with time *0 min* being the time of completion of the injection.

Intra-operative vital parameters of blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation were monitored initially at *5 min* interval until *15 min* and then at *15 min* interval until completion of surgery. The quality of analgesia was assessed every hour post-operatively for *24 hours* in the recovery room and in surgical ward by attending nurse using VAS scale (1–10): zero was considered as no pain, 1–3 as mild pain, 4–6 as moderate pain, and 7–10 as severe pain. At the score of 4, nursing staff was directed to administer injection diclofenac sodium *75 mg* intramuscularly. Duration of analgesia was calculated from the time of local anesthetic injection to the time of first analgesic requirement. All patients were observed for any side effects such as nausea, vomiting, bradycardia and hypotension and complications of supraclavicular block like pneumothorax, hematoma, Local anesthesia toxicity, and post block neuropathy in the intra and post-operative periods and treated accordingly.

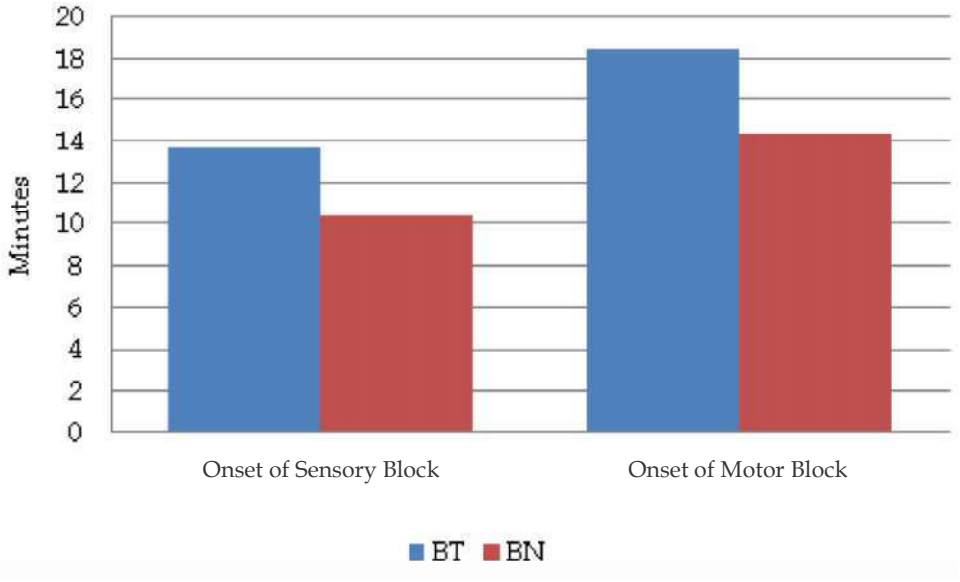
Results

Patients of both groups were comparable with respect to the demographic profile for age, sex distribution, ASA physical status. The baseline vital parameters of heart rate, systemic blood pressure, and oxygen saturation were comparable between the groups. Intra-operatively, hemodynamic changes did not reveal any significant difference between the groups and all patients remained hemodynamically stable throughout the surgery. Onset time of sensory block (*10.46 ± 1.5 min* vs. *13.66 ± 2.5 min*) and motor block (*14.4 ± 2.5 min* vs. *18.46 ± 3.5 min*) in Group BN was significantly faster than Group BT ($p < 0.001$), showed as in (**Table 1**), along with (**Graphics 1** and **2**).

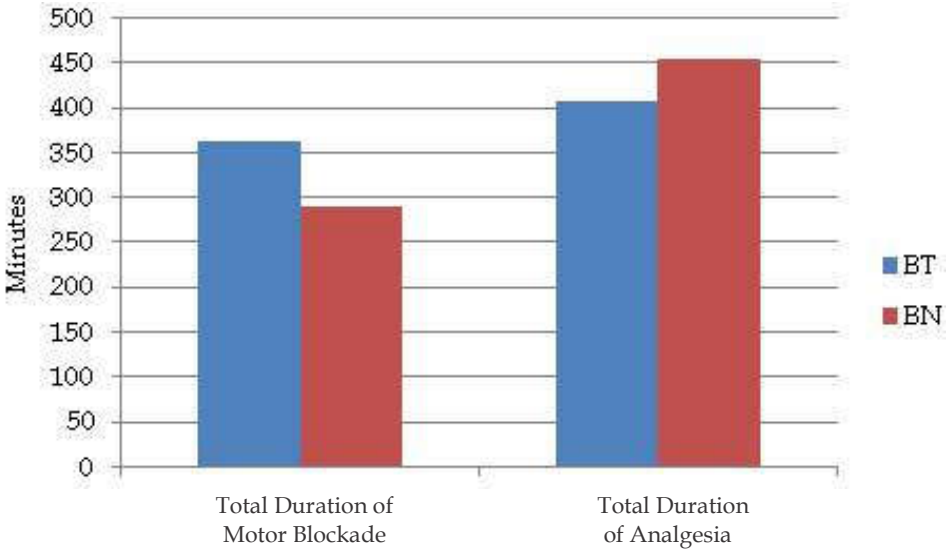
Table 1:

	Onset of sensory blockade	Onset of motor blockade
Group BT	13.66 +/- 2.5	18.46 +/- 3.5
Group BN	10.46 +/- 1.5	14.4 +/- 2.5
	Total duration of motor blockade	**Total duration of analgesia**
Group BT	*363.07 min/6.05 hrs*	*409.13 min/6.8 hrs*
Group BN	*291.4 min/4.8 hrs*	*456.00 min/7.6 hrs*

The mean duration of motor block was *291.4 min* in patients of Group BN when compared to Group BT (*363.07 min*) and the difference was statistically



Graph 1:



Graph 2:

significant ($p < 0.001$). The duration of analgesia in patients of Group BN was *456.00 min* and in patients of Group BT was *409.13 min* with p – value = 0.003. No side effect was seen in either Group.

Discussion

Brachial plexus blockade is commonly performed regional anesthetic technique for forearm and hand surgeries, and its blockage provides good surgical anesthesia. There are several advantages of regional anesthesia over general anesthesia in terms of safety, effective pain relief, and early discharge from the recovery room. However, additional analgesics are required for relieving the post-operative pain,[12,13,14,15] as the duration of action of currently available Local anesthetic agent is short. Increasing the dose of Local anesthetic agents may prolong the Duration of action[16] but may also increase the risk of LA systemic toxicity.[17]

Different opioids have been added to local anesthetic to improve the quality and duration

of post-operative analgesia of peripheral nerve blocks.[18] Many previous studies have attempted to determine whether the addition of opioid to local anesthetics would improve the clinical efficacy of peripheral nerve blocks and demonstrated that different types of opioids act well on peripheral nerve through stimulation of opioid receptor, but they were associated with unacceptable adverse effects. Tramadol and fentanyl were commonly used as adjuvant to local anesthetic drug in brachial plexus block.[19] Systemic review of various adjuvants for brachial plexus block suggested that the nalbuphine appeared to possess greater analgesic efficacy with minimal adverse effects.

Nalbuphine hydrochloride, a potent analgesic,[9] acts as a Kappa agonist and partial mu antagonist.[9,10,11] Its affinity to κ-opioid receptors results in sedation, analgesia, and cardiovascular stability with minimal respiratory depression.[9,10]

Tramadol is an analgesic with μ mixed opioid and non-opioid activity. It inhibits the reuptake of norepinephrine (NE) and serotonin from the nerve endings and potentiates the effects of local anesthetics when mixed together in peripheral regional nerve block. It has less respiratory depressant effect due to weak μ receptor affinity.[6]

Youssef and ElZayyat[20] compared the effect of nalbuphine with tramadol as adjuvants to lidocaine in intravenous regional anesthesia and concluded that both nalbuphine and tramadol were comparable, but nalbuphine was more effective than tramadol for prolonging the duration of post-operative analgesia.

Abdelhaq and Elramely[21] also used *20 mg* nalbuphine as adjuvant to *25 ml* of 0.5% bupivacaine for supraclavicular brachial plexus block for upper arm surgeries and concluded that nalbuphine has significantly increased the duration of both sensory and motor block along with prolonged post-operative analgesia.

In the present study, we observed the statistically significant enhanced onset of action, enhanced duration of motor block along with duration of analgesia with addition of nalbuphine to 0.5% bupivacaine as compared to tramadol in brachial plexus block. This prolongation of anesthetic effect and analgesia could be secondary to the stimulation of kappa receptors by nalbuphine, which inhibits release of neurotransmitters for pain such as substance P. The benefits of nalbuphine were not associated with any hemodynamic variability or any adverse event.

Conclusion

Nalbuphine is superior to tramadol in terms of onset of action, duration of motor blockade and post-operative duration of analgesia when added as an additive to bupivacaine in supraclavicular brachial plexus block.

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Conflicts of interest: There are no conflicts of interest.

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Original Research Article

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A Comparative Study between Ropivacaine with Clonidine and Bupivacaine with Clonidine in Brachial Plexus Blocks in Upper Limb

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Abstract

Introduction: The supraclavicular brachial plexus block provides anaesthesia of entire upper extremity in most consistent manner. Brachial plexus blockade for upper limb surgeries is advantageous as the effect of drug is limited to the part of the body to be operated upon. *Materials and Methods:* The present study titled "A comparative study of Ropivacaine + Clonidine with Bupivacaine + Clonidine in supraclavicular brachial plexus block" was carried out at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda District, Telangana State. It was a prospective and randomized study. Sixty patients of age group between 18 and *70 years* admitted between *August 2018* and *November 2018* were selected for the study. These patients were undergoing elective operative procedures for upper limb surgeries (i.e., elbow, forearm and hand surgeries). Exclusion criteria included patient's refusal, history of bleeding disorders or patients on anticoagulant therapy, peripheral neuropathy, local infection, respiratory disease, or known allergy to local anesthetic drugs. Each patient was visited pre-operatively and the procedure was explained and informed written consent was obtained. Investigations like Hemoglobin, Bleeding time, Clotting time, blood grouping, random blood sugar, blood urea, serum creatinine, bleeding time, clotting time, chest x-ray, ECG were done. *Results:* The present study was conducted on 60 consenting patients aged between 18 and 70 years. Group RC received *30 ml* of 0.5% Ropivacaine + clonidine (*30 mcg*). Group BC received 30 ml of 0.5% Bupivacaine + clonidine (*30 mcg*) for brachial plexus block by supraclavicular approach. The minimum age in both groups was *18 years*. The maximum age in both groups was *60 years* and *65 years* respectively. The mean age in group BC were 31.20 ± 12.59 and RC were 32.00 ± 13.17 respectively. There was no significant difference in the age of patients between the Group BC and Group RC. Both groups were similar with respect to age distribution ($p > 0.05$). *Conclusion:* From our study, we concluded that addition of Clonidine (*2 µg/kg*) to 0.5% Ropivacaine in supraclavicular brachial plexus block has advantages compare to bupivacaine with clonidine Faster onset of analgesia, sensory and motor blockade.

Keywords: Supraclavicular brachial plexus block; Ropivacaine; Clonidine.

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Introduction

The supraclavicular brachial plexus block provides anesthesia of entire upper extremity in most consistent manner. Brachial plexus blockade for upper limb surgeries is advantageous as the effect of drug is limited to the part of the body to be operated upon.[1]

A commonly used drug for this technique is bupivacaine 0.5% which is a well-established long acting local anesthetic, which like all amide anesthetics has been associated with cardiotoxicity

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when used in high concentration or when accidentally administered intravascularly.[2]

As with other fields, regional anesthesia too, has undergone major developments, both in techniques and drug availability. Ropivacaine was thus developed after it was noted that bupivacaine was associated with significant number of cardiac arrests. Ropivacaine is a new long acting local anesthetic drug belonging to the amino amide group. Ropivacaine and bupivacine belong to pipecoloxylidides group of local anesthetics. It is a pure S(-) enantiomer, unlike Bupivacaine, which is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.[3,4]

Addition of adjuvant drugs to the local anesthetic might improve quality, onset and duration of block and decrease post-operative analgesic requirement and systemic side effects.[2] Opioids, clonidine, ketamine and prostigmine have been added to local anesthetics and injected extradurally, intrathecally or in nerve plexuses for a more intense and prolonged analgesia.[5–8] Opioids are commonly added to local anesthetic solutions to increase intensity and duration of anesthesia by acting on opioid receptors present on the nerve terminals.[9,10] However, fentanyl has some side effects as vomiting and respiratory depression.[7] Clonidine is a selective Alpha-2 adrenergic agonist with some Alpha-1 agonist property. In clinical studies, the addition of clonidine to local anesthetic solution improved peripheral nerve blocks by reducing the onset time improving the efficacy of the block during surgery and extending post-operative analgesia.

Aims and Objectives

The present study is aimed to compare the effects of 0.5% Ropivacaine with clonidine (*30 mcg*) and 0.5% Bupivacaine with clonidine (*30 mcg*) in supraclavicular brachial plexus block in terms of:

- The onset of blockade–sensory and motor blockade
- Duration of the blockade–sensory and motor blockade
- Quality of the block

Materials and Methods

The present study titled "A comparative study of Ropivacaine + Clonidine with Bupivacaine + Clonidine in supraclavicular brachial plexus block" was carried out at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda District, Telangana State. It was a prospective and randomized study.

Sixty patients of age group between *18* and *70 years* admitted between August *2018* and *November 2018* were selected for the study. These patients were undergoing elective operative procedures for upper limb surgeries (*i.e.*, elbow, forearm and hand surgeries).

Exclusion criteria included patient's refusal, history of bleeding disorders or patients on anticoagulant therapy, peripheral neuropathy, local infection, respiratory disease, or known allergy to local anesthetic drugs.

Each patient was visited pre-operatively and the procedure was explained and informed written consent was obtained. Investigations like Hemoglobin, Bleeding time, Clotting time, blood grouping, random blood sugar, blood urea, serum creatinine, bleeding time, clotting time, chest *X*-ray, ECG were done.

Each patient was randomly assigned to one of the two groups of 30 patients each, Group BD or Group RD by a computerized randomization.

Group – BC *i.e.*, *30 ml* of Bupivacaine group received 0.5% Bupivacaine according to body weight + clonidine (*30 mcg*).

Group – RC *i.e.*, *30 ml* of Ropivacaine group received 0.5% Ropivacaine according to body weight + clonidine (*30 mcg*).

Each patient was made to lie supine without a pillow, arms at the side, head turned slightly to the opposite side with the shoulders depressed posteriorly and downward by moulding the shoulders over a roll placed between the scapulae. The supraclavicular area was aseptically prepared and draped. The anesthesiologist stands on the side of the patient to be blocked. The patients were administered brachial plexus block by supraclavicular approach under strict aseptic precautions. The injection site was infiltrated with *1 ml* of lidocaine 2% subcutaneously. A nerve stimulator with 50 mm stimuplex needle is used to locate brachial plexus. The location end point being a distal response with an output of 0.4 *mA*. During injection, negative aspiration was performed every *6–7 ml* to avoid intravascular injection. A *3-min* massage was performed to facilitate an even drug distribution.

Time of onset of sensory block was recorded using pinprick in skin dermatomes C4-T2. The same observer assessed the motor block at the

same time.

Onset of sensory block was from the time of injection of drug to time of loss of pain on pinprick. Onset of motor block was from the time of injection to time of complete loss of movement.

Sensory block was assessed by pinprick with a short bevelled 23G needle as:

Grade 0 – Sharp pin prick felt.

Grade 1 – Analgesia, dull sensation felt.

Grade 2 – Anesthesia, no sensation felt.

Motor block was graded according to the modified Bromage scale:

Grade 0 – Normal motor function with full extension and flexion of elbow, wrist, and fingers.

Grade 1 – Decreased motor strength, with ability to move only fingers.

Grade 2 – Complete motor block with inability to move elbow, wrist, and fingers.

Duration of sensory blockade was the time in minutes from the onset of analgesia to the recurrence of pain to pin prick. Duration of motor blockade was the time in minutes from the onset of paresis to the recurrence of motor movements.

The quality of the block was graded according to whether opioids were used during intra operative period (Grade II) or if adjuvants of any kind were not used throughout the surgery (Grade I). For the patients who were anxious and perturbed by the sensation of touch on the operating limb, Inj. Fentanyl *50 mcg* IV was administered. The blocks that required conversion to general anesthesia were excluded from the study.

The heart rate, oxygen saturation and mean arterial pressure were recorded. Patients were watched for complications such as bradycardia, convulsions, restlessness, disorientation or drowsiness. All the values were expressed as mean ± standard deviation. Statistical comparison was performed by student's *'t'* test and Chi-Square test.

A *p* - value of > 0.05 was considered to be statistically not significant, a *p* - value 0.05 as statistically significant, a *p* - value of < 0.01 as statistically highly significant and a *p* - value of < 0.001 as statistically very highly significant.

Results

The present study was conducted on 60 consenting patients aged between *18* and *70 years*. Group RC received *30 ml* of 0.5% Ropivacaine + clonidine (*30 mcg*). Group BC received 30 ml of 0.5% Bupivacaine + clonidine (*30 mcg*) for brachial plexus block by supraclavicular approach.

Table 1: Age distribution of patients

Age in Years	Group BC (Bupivacaine + Clonidine)		Group RC (Ropivacaine + Clonidine)	
	Number of Patients	Percent	Number of Patients	Percent(%)
18–24	5	16.67	10	33.33(%)
25–31	12	40	10	33.33(%)
32–38	6	20	2	6.67(%)
39–45	2	6.67	2	6.67(%)
46–52	2	6.67	3	10.00(%)
53–59	1	3.33	1	3.33(%)
60–66	2	6.67	2	6.67(%)
Total	30	100.00	30	100.00(%)
Mean ± SD	31.20 ± 12.59		32.00 ± 13.17	
Minimum	18		18	
Maximum	60		65	

$\chi 2 = 2.348$, p = 0.8850

Table 1 shown in age distribution of the patients in both the groups. The minimum age in both groups was *18 years*. The maximum age in both groups was *60 years* and *65 years* respectively. The mean age in group BC were 31.20 ± 12.59 and RC were 32.00 ± 13.17 respectively. There was no significant difference in the age of patients between the Group BC and Group RC. Both groups were similar with respect to age distribution ($p > 0.05$) shown as in (**Tables 2–8**).

Table 2: Distribution of patients according their sex

Sex	Group BC		Group RC	
	Number of Patients	Percent	Number of Patients	Percent(%)
Male	18	60.00%	21	70.00%
Female	12	40.00%	9	30.00%
Total	30	100.00%	30	100.00%

$\chi 2 = 0.08208$, $p = 0.7745$

No significant difference was observed in sex distribution of the cases between two groups ($p > 0.05$).

Table 3: Showing the weight distribution in each group

Weight	Group BC		Group RC	
	Number of Patients	Percent	Number of Patients	Percent(%)
40–49	12	40	9	30(%)
50–59	11	36.67	15	50(%)
60–69	7	23.33	6	20(%)
Total	30	100	30	100(%)
Mean ± SD	52.93 ± 6.52		53.73 ± 5.45	
Minimum	40		42	
Maximum	68		62	

$\chi 2 = 1.121$, $p = 0.5710$

Table 4: Comparison of onset of sensory and motor blockade

Onset of Block (*min*)	Group BC				Group RC				
	Min	Max	Mean	SD	Min	Max	Mean	SD	
Motor	8	15	12.57	1.9205	7	13	8.07	1.5447	$p = 0.001$
Sensory	6	12	10.37	1.5313	5	12	6.93	1.8557	$p = 0.001$

Table 5: Duration of blockade (*min*)

Duration of Block	Group BC				Group RC				
	Min	Max	Mean	SD	Min	Max	Mean	SD	
Motor	370	480	431.33	32.56	340	480	415.33	36.11	$p = 0.07$
Sensory	390	520	480.33	20.13	380	500	469.67	25.15	$p = 0.07$

The two groups are compared according to their weight. This was statistically not significant ($p > 0.05$).

In Group BC the mean onset time of sensory blockade was 10.37 minutes and motor blockade were 12.57 minutes whereas in Group RC, the mean onset time of sensory blockade was 6.93 minutes and motor blockade were 8.07 minutes.

Onset of sensory and motor blockade was earlier in case of Group RC (Ropivacaine group) when compared with Group BC (Bupivacaine group). The p - value was < 0.01 which is statistically significant.

In group BC the mean duration of sensory blockade was 480.33 minutes and motor blockade were 431.33 minutes when compared to group RC, where sensory blockade duration was 469.67 minutes and duration of motor blockade 415.33 minutes.

The duration of sensory and motor blockade was similar in Group BC when compared to Group RC. There was no statistical difference between the two ($p > 0.05$).

Table 6: Quality of blockade

Class	Group BC	Group RC
1	20	22
2	10	8
Total	30	30

$\chi^2 = 0.31$, $p = 0.57$

In Group BC 20 patients needed no additional drug like opioids (Inj. Fentanyl *50 mcg* IV) when compared with Group RC where 22 patients didn't need any adjuvant. Adjuvants were used in 10 patients in group BC whereas 8 patients needed adjuvants in Group RC.

This is statistically not significant ($p > 0.05$).

Table 8: Mean duration of surgery in minutes

	Group BC				Group RC			
	Min	Max	Mean	SD	Min	Max	Mean	SD
Duration of Surgery	50	130	78.41	21.10	50	130	69.5	19. 3

$p = 0.15$

In group BC, the mean duration of surgery was 78.41 ± 21.10 minutes whereas in group RC the mean duration of surgery was 69.5 ± 19.3 minutes. The mean duration of surgery in Group BC was similar compared to Group RC. The p - value (0.15) was also not statistically significant.

Discussion

Regional anesthetic techniques are used for both operative anesthesia and for post-operative analgesia. They are becoming more popular as a result of advances in drugs, equipment, and improved techniques of anatomical localization, including nerve stimulator and ultrasonic location.[11]

Regional anesthetic techniques may be used alone or in combination with sedation or general anesthesia depending on individual circumstances.[12,13] The advantages of regional techniques include:

- Avoidance of the adverse effects of general anesthesia.
- Post-operative analgesia.
- Preservation of consciousness during surgery.
- Sympathetic blockade and attenuation of the stress response to surgery.
- Improved gastrointestinal motility and reduced nausea and vomiting.
- Simplicity of administration.
- Rapid mobilization of patient and early discharge decreases DVT.

- More economical for the patient.

The net effect of these features leads to a reduction in the incidence of major post-operative respiratory complication. The upper limb is well suited to regional anesthetic techniques and these remain among the most useful and commonly practiced peripheral regional techniques. Supraclavicular block offers dense anesthesia of brachial plexus for surgical procedures at or distal to the elbow. This approach provides perhaps the best overall efficacy of complete arm block from a single injection as the trunks/divisions of the brachial plexus are closely related at this point.[14,15,16]

For a long-time, the choice of local anesthetic for brachial plexus block was Bupivacaine, a long-acting amide local anesthetic. However, concerns about its high lipid solubility and high cardiotoxicity limited its use. With the advent of newer and safer long-acting amide local anesthetics such as Ropivacaine and Levobupivacaine, Bupivacaine has largely been replaced. Ropivacaine has lower lipid solubility and produces less central nervous toxicity and cardiotoxicity than Bupivacaine. It has been shown that Ropivacaine interferes with mitochondrial respiration and ATP synthesis less than both racemic bupivacaine and Levobupivacaine. Ropivacaine is thus gaining popularity over Bupivacaine for peripheral nerve blocks.[17,18]

There has been a search for an ideal adjuvant to local anesthetics for regional nerve block that prolongs the analgesia with lesser side effects. Several adjuncts have been described to decrease the time of onset to the block and to prolong the duration of the block. Drugs such as opioids, Dexmethasone, Tramadol, Neostigmine, Epinephrine, Dexmedetomidine and Clonidine have been used as adjuncts to brachial plexus blocks.[19]

Evidence regarding the analgesic benefit of opioid adjuncts remains equivocal. There appears to be no advantage for reduced adverse effects by the peripheral administration of opioid analgesics. Nausea, vomiting and pruritis occurred even with the peripheral administration of opioids.

Sufficient data is not available to allow the recommendation of tramadol and neostigmine as adjuncts to local anesthetics in brachial plexus block. Clonidine enhances both sensory and motor blockade of neuraxial and peripheral nerves after injection of local anesthetic solutions. There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. These mechanisms are centrally mediated analgesia, alpha-2-adrenoreceptor mediated vasoconstriction, attenuation of inflammatory response and direct action on peripheral nerve. Clonidine possibly enhances or amplifies the sodium channel blocking action of local anesthetics by opening up the potassium channels resulting in hyperpolarization, a state in which the cell is unresponsive to excitatory input.[20]

The present study is undertaken to compare the onset, duration of sensory and motor block and the quality of block achieved by Bupivacaine with clonidine and Ropivacaine with clonidine. Supraclavicular brachial plexus block was administered in 60 patients selected randomly for elective and emergency surgeries. 0.5% Bupivacaine was administered with clonidine (*30 mcg*) to 30 patients selected randomly and 0.5% Ropivacaine was administered with clonidine (*30 mcg*) to 30 patients selected randomly.

Conclusion

From our study, we concluded that addition of Clonidine (*30 mcg*) to 0.5% Ropivacaine in supraclavicular brachial plexus block has following advantages compare to bupivacaine with clonidine Faster onset of analgesia, sensory and motor blockade:

1. Less cardiac Toxicity.
2. No significant Difference in hemodynamic parameters (pulse rate, Blood pressure; SpO_2 and respiratory rate) and no significant side effects and complications.

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Original Research Article

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A Retrospective Study of Predictors of Mortality in H1N1 Influenza Associated Deaths in a Tertiary Care Hospital

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Abstract

This study aims is to identify the predictors of mortality in Swine flu associated deaths and to formulate protocols and guidelines for the future management of Swine flu patients in case of inter-hospital patient transfer, risk stratification and optimization of other co-morbid conditions. *Design:* Retrospective Descriptive Study. *Materials and Methods:* Patients who were admitted in the hospital from September 2017 to March 2018 and September 2018 to March 2019 were included in the study as two separate groups. The data was retrospectively collected from the Medical Records Department (MRD). Information regarding age/ sex, clinical presentation, laboratory findings, organ failures, arterial blood gas parameters, Chest X-ray, duration of ICU stay, need for mechanical ventilation and pre-existing co-morbidities was collected. *Analysis:* Categorical variables were presented in numbers. The data was entered in MS Excel spread sheet and analysis was done using SPSS version 22.0 by calculating percentages. *Conclusion:* Old age, presence of co-morbidities, late admission to a tertiary care hospital, inter-hospital transfer, low Pao2/Fio2 ratio at the time of admission were identified as the key factors for early mortality in H1N1 Influenza patients. *Recommendation:* Better protocols are to be formulated for the management of Swine flu positive patients in cases of inter-hospital patient transfer, risk stratification and optimization of other co-morbid conditions.

Keywords: Inter-hospital transfer; Co-morbidities; Duration of illness; Q-sofa score; Murray score.

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Introduction

We conducted our study on Swine flu patients who were admitted in PGIMER and RML Hospital earmarked for treating critically ill patients of Swine flu for two consecutive years from *September 2017* to *March 2018* and *September 2018* to *March 2019*.

This study was conducted to understand the contributing factors for Swine flu associated mortality of patients. There are very few studies on mortality associated with H1N1 virus related disease in India. Hence, we are conducting this study to assess the predictors of mortality in Influenza caused by H1N1 virus.

Aims and Objectives

Aim of the study was to identify the contributing factors common with mortality cases of Swine flu and to do risk stratification of these patients in case

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of inter-hospital and intra-hospital transfer to ICU. Also to find out modifiable contributing factors of mortality to achieve reduction in mortality.

Materials and Methods

Patients reported to this hospital both from community as well as inter-hospital transfer cases. An especially dedicated fever clinic is managed in RML Hospital to identify Swine flu patients at the initial course of illness. The annual OPD attendance of patients with respiratory illness is 2500 in RML Hospital, New Delhi.

The patients attending fever clinic were categorized according to the guidelines of Ministry of Health and Family Welfare, India for Swine flu as per which patient may fall into Category A to C depending upon the spectrum of disease.[1]

Category A

Patients with mild fever plus cough, sore throat with or without headache, diarrhea, body ache, and vomiting did not require Oseltamivir and were managed symptomatically at home. No testing of the patient for Influenza was required.

Category B

1. In addition to the signs and symptoms mentioned under Category A, if the patient had severe sore throat and high grade fever, home isolation and Oseltamivir were required.
2. In addition to all the signs and symptoms mentioned under Category A, patients having one or more of the following high-risk conditions were treated with Oseltamivir:
    (a) Children with mild illness but with predisposing risk factors.
    (b) Pregnant women.
    (c) Persons aged *65 years* or older.
    (d) Patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS.
    (e) Patients on long-term cortisone therapy.

Tests for Influenza are not required for Category B (1) and (2). Broad Spectrum antibiotics as per the Guideline for Community Acquired Pneumonia (CAP) were prescribed.

Category C

In addition to the above signs and symptoms of Category A and B, if the patient had one or more of the following:

(a) Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails.

(b) Children with influenza like illness who had a severe disease as manifested by the red flag signs (somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc.).

(c) Worsening of underlying chronic conditions.

All these patients mentioned above in Category C required testing, immediate hospitalization and treatment.

I. All the cases of fever with pneumonia who attended the fever clinic were kept under suspicion of being Swine flu positive unless proven negative by laboratory reports. These patients were shifted to a separate dedicated High Dependency Unit by the Department of Medicine. However, the patients who were diagnosed Swine flu positive by RT PCR test done in the laboratory and requiring ventilator support were referred to Swine flu ICU of the hospital.

II. Patients in critical conditions referred from other hospitals of NCR and Delhi were triaged in the casualty of RML Hospital by qSofa Scoring and were sent to either the High Dependency Unit or the Swine flu ICU depending on the qSOFA.[2] Score Quick(q)SOFA Score: Uses three criteria, assigning one point for low Blood Pressure (Systolic Blood Pressure ≤ 100 *mm Hg*), high Respiratory Rate (≥ 22 breaths/minute) or altered mentation (Glasgow coma scale < 15). The score ranges from 0–3 points. The presence of 2 or more qSOFA points near the onset of infection.

Those requiring invasive mechanical ventilation were shifted to Swine flu ICU whereas those who could be managed with supplemental oxygen therapy and non-invasive methods of ventilation (CPAP/Bi PAP) were sent to the High Dependency Unit (HDU).

The Swine flu ICU is a six bedded ICU. The patients in Swine flu ICU were managed by

anesthesiologists team of Consultants and resident doctors, nurses and technicians. On admission to ICU the severity of patient's lung injury was assessed on the basis of Murray scores[3] apart from clinical and laboratory examination. This allowed the practitioner to form decision on the course of management of the patients.

The data was retrospectively collected from the Medical Records Department (MRD). Patients who were admitted in the hospital from *September 2017 – March 2018* and *September 2018 – March 2019* were included in the study as two separate groups. Information regarding age/ sex, clinical spectrum, laboratory findings, organ failures, arterial blood gas parameters, chest *X*-ray, duration of ICU stay, need for mechanical ventilation and pre-existing co-morbidities was collected.

Category C patients with Influenza like symptoms diagnosed in Casualty or fever clinic were admitted to Swine flu HDU of RML Hospital. A sample of throat swab and nasal swab was collected for all the suspected cases of H1N1 Influenza on the day of admission by a trained doctor before administration of the anti-viral drug.

Sample Collection

A swab was inserted into one nostril straight back (not upwards) and horizontally to the nasopharynx up to the measured distance on the swab handle. The swab was rotated up to *5 times* and held in place for *5–10 seconds* to collect sample material. The swab was removed and insert into a vial containing *1–3 ml* of viral transport media containing, protein stabilizer, antibiotics to discourage bacterial and fungal growth, and buffer solution. The specimens were kept at *4 degree Celsius* until transported for testing. The sample was transported to the designated laboratory of Microbiology Department (BSL Level 2), RML Hospital or National Centre for Disease Control (NCDC) within *24 hours* which is within the acceptable deadline of *4 day* Those who were admitted as suspected cases but came out to be negative were excluded from the study.

The initial management of the confirmed cases included Tablet Oseltamivir, broad spectrum antibiotics which were administered empirically to the patients at the time of admission and further management was done according to the culture and sensitivity reports along with the supportive treatment. Ventilatory settings were done as per the protocol for ARDS management. Patients requiring prolonged ventilator support and those with high FiO_2 requirement were tracheostomised; those with shock were started on inotropes.

Statistical Analysis

Categorical variables were presented in numbers. The data was entered in MS Excel spread sheet and analysis was done using SPSS version 22.0 by calculating percentages.

Type of study

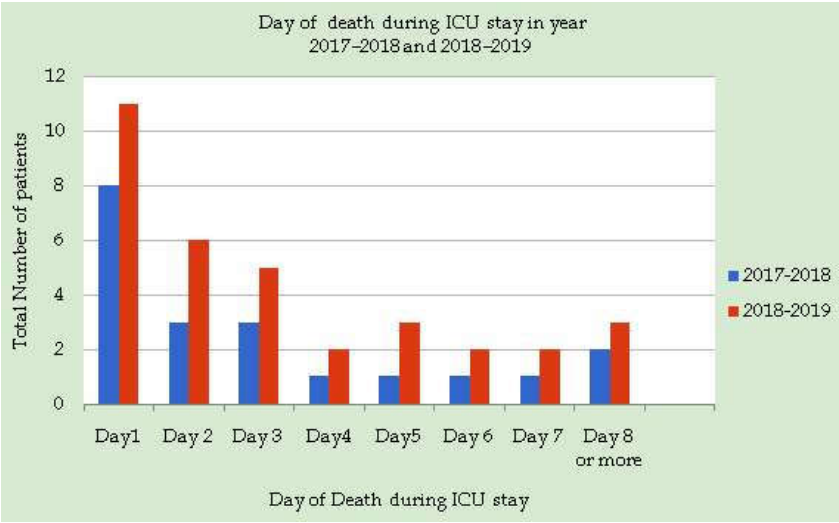
Retrospective Descriptive Study.

Results

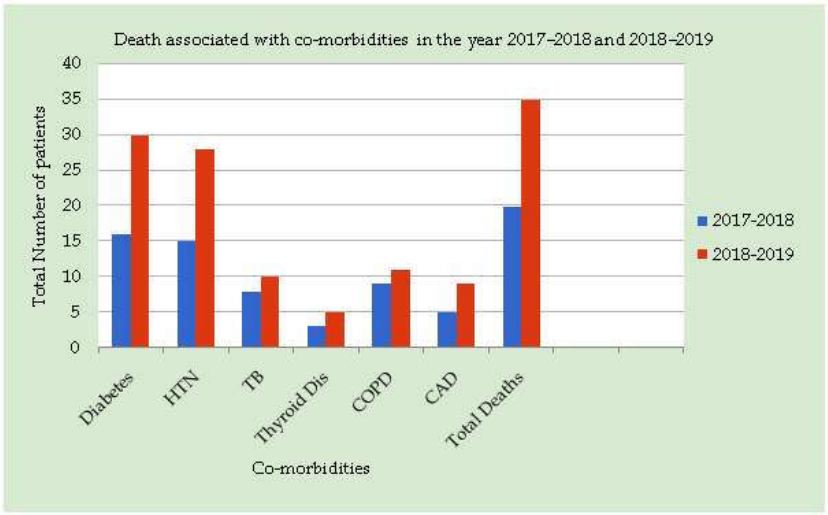
Out of 40 confirmed cases of Swine flu who required admission 20 (50%) deaths occurred in the *year of 2017–18* and 35 out of 43 (81%) admitted confirmed cases died in the *year of 2018–19*. There were almost equal no of male and female patients in both the years. Most of the patients were more than *50 years of age*. Majority of the deaths occurred within *24 hr* of admission, *i.e.*, 40% in the *year of 2017–18* and 31.4% in the *year 2018–19*.

Most common symptoms on presentation was cough (100%), fever (100%), breathlessness (60%), followed by URI symptoms such as sore throat (35%), headache (20%), fatigue (16%), common cold (12%), joint pain (8%). Other symptoms like vomiting and diarrhea (8.9%), bleeding (5.3%) were present in a lesser number of patients. Majority of the patients (85%) had more than one co-morbid conditions like diabetes, hypertension, pulmonary tuberculosis, coronary artery disease, chronic obstructive pulmonary disease, hypothyroidism. Only 5% of patients didn't have any co morbidities.

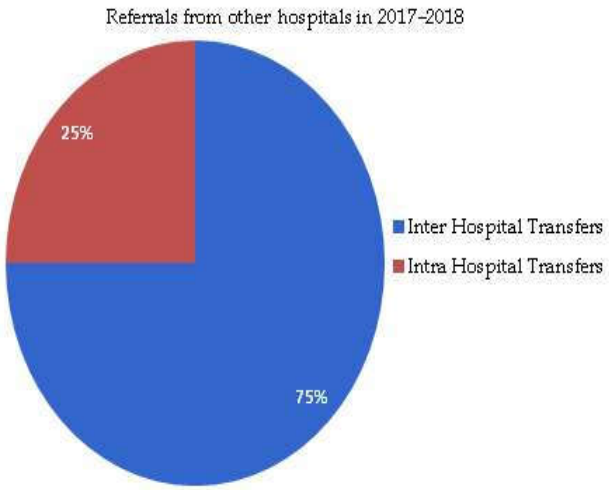
Mean duration of symptoms before admission to any hospital was *15 days*. 75% of patients in 2017–18 and 80% in 2018–19 were inter-hospital transfers. All the patients required mechanical ventilation, out of which 70% required PEEP more then 12. All the expired patients had a low PaO_2/FiO_2 ratio (< 300). 60% of patients had acidosis at the time of admission in 2017–18, whereas acidosis was present in 54.2% patients in 2018–19 at the time of admission. On radiological evaluation 70% of cases had bilateral infiltrate and 30% had unilateral infiltrate in 2017–18, whereas 85% had bilateral infiltrates and 15% had unilateral infiltrate in 2018–19 showed in (**Graphs 1–8).**



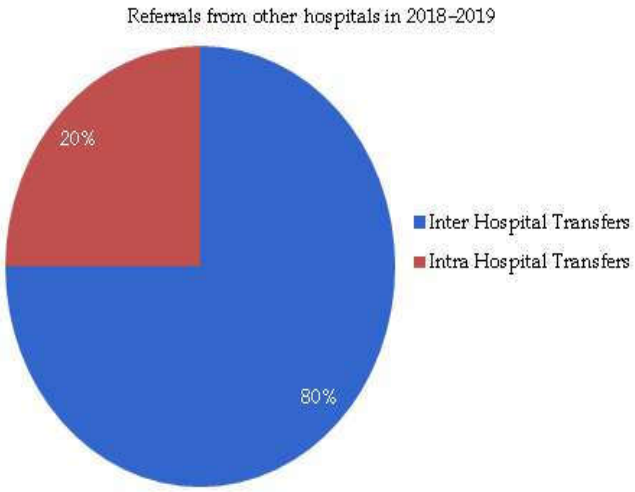
Graph 1: Showing day of death during ICU stay



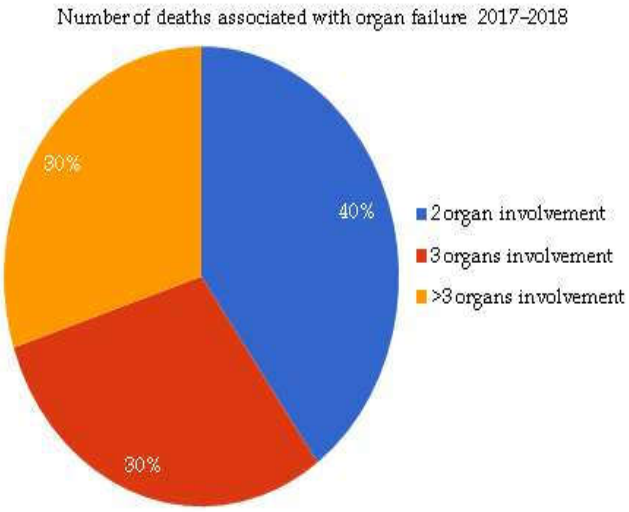
Graph 2: Showing co-morbidities associated with H1N1 Influenza



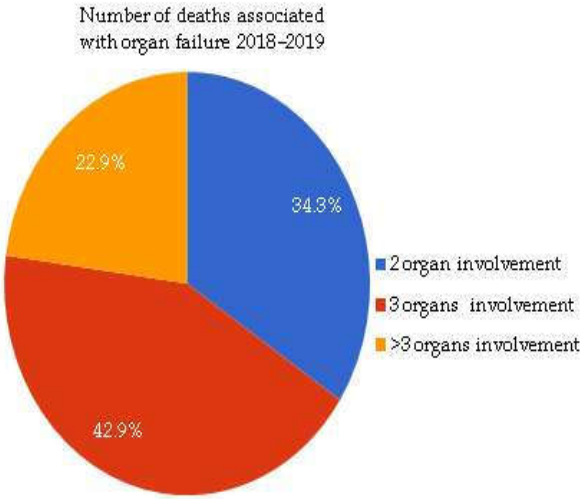
Graph 3: Showing Referrals from other hospitals in 2017–2018



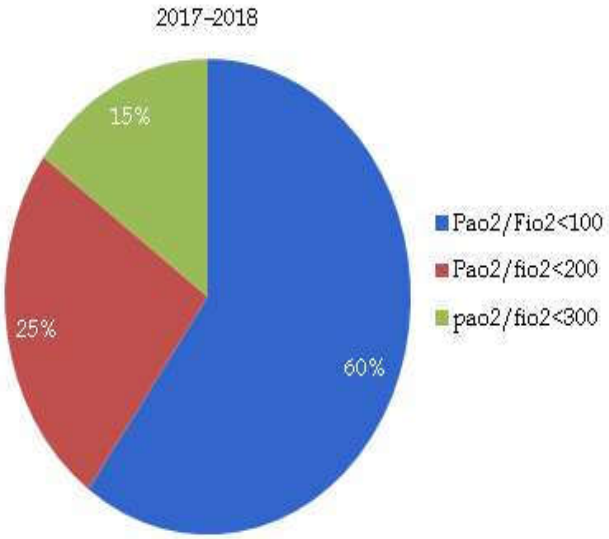
Graph 4: Showing Referrals from other hospitals in 2018–2019



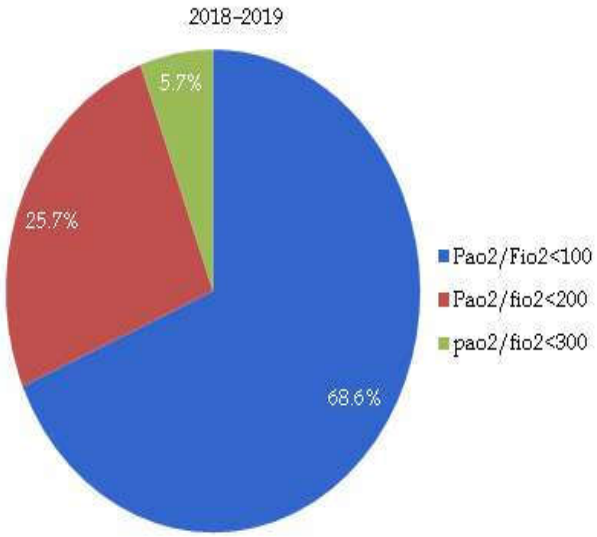
Graph 5: Showing Number of deaths associated with organ failure in 2017–2018



Graph 6: Showing number of deaths associated with organ failure in 2018–2019



Graph 7: PaO_2/ FiO_2 ratio distribution in 2017–2018 in mortality cases



Graph 8: PaO_2/ FiO_2 ratio distribution in 2018–2019 in mortality cases

Discussion

We studied the clinical profiles of patients who died of H_1N_1 in the Swine flu ICU and HDU during the period of March–September 2017–2018 and 2018–19 to identify the predictors of mortality in Swine flu patients. 20 deaths were reported in the *year 2017–18* out of 40 confirmed cases of Swine flu where as there were 35 deaths reported out of 43 cases in the *year 2018–19*. Highest number of deaths belonged to the age group of more than *50 years* and was equally distributed between males and females in both the study years. These findings were consistent with a previous study on hospitalized patients with H1N1 influenza in the *year 2009*[4]

The average duration of symptoms before hospital admission was one to *two weeks*. According to Ministry of health and family welfare (MOHFW) guidelines, patients with symptoms suggestive of seasonal influenza should have attended the fever clinic immediately at RML Hospital as it is the nodal center for diagnosis and management of Swine flu. However, in this study we found substantial delay in admission to our hospital and this worsened the prognosis of patients. It has been found in previous studies that delay in hospital transfer significantly increases mortality and morbidity of patients further[5] 86 percent patients were referred from private hospitals or managed by local practitioners initially which is not according to guidelines laid

down by MOHFW, Delhi. In this study, **Graph 3** and **Graph 4** shows number of referral cases from other hospitals to RML Hospital in the year 2017–2018 and 2018–2019.

When no improvement of the symptoms was found after a few days of treatment, these patients were referred to our center for further management. Inter hospital transfer plays a huge role in increasing the mortality as concluded by case control study in 2008, where patients admitted to ICU from another hospital have higher hospital mortality and longer stay than those admitted from the OPD or emergency department.[6]

In a single center retrospective study in 2018 it was concluded that critically ill patients may not benefit from inter-hospital transfer, instead may be harmed by the potential complications and expense of transfer.[7] Majority of these patients who were transferred from other hospitals were in severe ARDS, had developed secondary bacterial infections, and had worsening of underlying co-morbid conditions, all of which could have contributed to early mortality following admission to our hospital.

Majority of the patients who died of H_1N_1 had more than one co-morbid conditions as shown in **graph 2**, the most common one being diabetes mellitus followed by hypertension similar to an Indian study on pandemic Influenza A in the *year 2009*.[8] Chronic pulmonary diseases like COPD, pulmonary tuberculosis were present in a less number of patients in contrast to a study,[9] where majority of patients admitted with Swine flu had COPD and bronchial asthma. Due to underlying co-morbid conditions these patients have a compromised immune system which will promote rapid increase in viral load and hence delaying response to treatment and worsening of the co-morbid condition.[10,11]

Conclusion

More emphasis on preventive aspect like public awareness about H1N1 influenza illness and ways of preventing it needs to be done. Need of proper co-ordination between private hospitals and Nodal centers for management of Swine flu patients. The private hospitals are accountable in inter-hospital transfer of patients. A proper format needs to be devised for inter-hospital transfer of patient. The format should mention the reason for transfer and condition of patient at the time of transfer. Most of the patients are transferred because of monitory conditions of patient. A decision to subsidize the treatment of H1N1 patients in private hospital needs to be done to prevent transfer of patient in MODS and critical conditions.

Key Message

More emphasis should be on preventive aspect like public awareness about H1N1 Influenza illness and ways of preventing it needs to be done. There is a need of proper co-ordination between private hospitals and Nodal centers for management of Swine flu patients. A proper format needs to be devised for inter-hospital transfer of patient. The format should mention the reason for transfer and condition of patient at the time of transfer.

Acknowledgement

We would like to thank Dr. Shipra, Dr. Archana, Dr, Sagari Senior Residents of Department of Anesthesiology for their guidance and the nursing staff ANS sister Sarada Ravindran, sister incharge Jessy Antony, sister Bindu Ajith and Sister Sudesh bala of Swine flu ICU and Medical Records Department of PGIMER, Dr RML Hospital for their cooperation and support.

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Original Research Article

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Factors Considered by Final Year MBBS Students in Selecting Anesthesia as a Career Choice: A Questionnaire Based Study

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Abstract

Background: Smooth functioning of countries healthcare services require balanced distribution of physicians among different specialities. Each country needs to examine the factors influencing career specialty preference which will be helpful in future recruitment process. *Aims:* To assess the awareness and attitude towards anesthesiology as a career option and the factors which influence in making such a choice. *Methods:* A cross-sectional study was conducted on final year MBBS students in Navodaya Medical College, Raichur. A semi-structured, self-administered questionnaire copy was distributed to a total of 113 final year MBBS students and results were analyzed using SPSS version IBM 22. *Results:* The most preferred specialty was General Medicine (18.45%), followed by general surgery (15.53%) and orthopedics (14.56%). Among males the most preferred specialty was general medicine (27.12%) and among females obstetrics and gynecology (27.27%) was the most preferred specialty. The most common reason for not choosing anesthesia as a career choice was lack of recognition by patients (24.71%) and the most common reason behind making a career choice was personal interest (19.42%). 30.8% students found that anesthesia as a specialty was interesting and life saving and 37.5% students found that anesthesia posting was interesting and important. *Conclusion:* With only 2% students choosing anesthesia, it is vital to provide adequate aids and emphasize on the positive aspects of anesthesia among the undergraduates to create interest in anesthesiology as a career choice.

Keywords: Anesthesia; Career choice; MBBS students.

How to cite this article:

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Introduction

The specialty of anesthesiology which was confined to the operating room in the past has now widened its scope and includes ICU management, trauma, acute and chronic pain management. Inspite of its improved scope, the number of students preferring anesthesia as specialty is still significantly low.[1] The choice of career specialty made by graduating students and factors involved in making a choice have an impact on the healthcare services of the country. Studies on speciality preference are helpful to identify the possible influencing factors, which will provide valuable information to medical workforce planners in formulating future educational programmes especially when there is undersupply of doctors.[2,3]

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During the course of medical education, students are exposed to a wide range of specialities, and the exposure may significantly affect the career preference. Many factors influence the choice of career and include personal preferences, work environment, awareness and knowledge about the scope of subject and practice hours. Gender is another important factor in career choice and females usually choose pediatrics and obstetrics and gynecology.[2]

This study is aimed to assess the awareness and attitude towards anesthesiology as a career option and the factors which influence in making such a choice.

Materials and Methods

This study was conducted on final year MBBS students of Navodaya Medical College, Raichur, Karnataka. After obtaining approval from the hospital ethical committee, a brief talk on the study was given to the students and informed consent was obtained. A semi-structured, self-administered questionnaire copy was then administered to a total of 113 MBBS students in March 2019, who had undergone their undergraduate training in anesthesia. The questionnaire was designed to elicit sociodemographic characteristics, preference about specialization, reason for not choosing anesthesia as a career, possible factors that affected the choice of speciality and perception about anesthesia.

The questionnaire was designed in five parts. The first part included demographic data. The second part of the questionnaire was to find the preferred speciality following their graduation. It included a list of 12 commonly preferred specialities including anesthesia. Top three choices in the order of preference were asked. It also had an option of not decided and others. The third part was reason for not choosing anesthesia as their preference. It had nine common reasons listed and an option to mention any other reason than the above listed. The fourth part of the study contained a list of 14 common factors that influence the students in making a career choice. The top three preferred factors were asked. It also included an option of listing any other factors. The fifth part of the questionnaire was about the perception of anesthesia before and after attending the postings.

After collecting data from self reporting questionnaire, it was coded and manually entered into the computer for statistical analysis. The analysis was done using the Statistical Package for Social Sciences Software (SPSS, version IBM 22). Data analysis was performed using frequency and diagrams.

Results

The total number of final year MBBS students in our institute was 113. Of this 103 students participated in the study, consisting of 44 females (42.71%) and 59 males (57.28%). The mean age of respondents was 21.47. Overall the most preferred career choice was General Medicine (19 students, 18.45%). It was followed by general surgery (16 students, 15.53%) as the second preferred choice and orthopedics (15 students, 14.56%) as the third preferred choice, 7 students have not yet decided their specialty choice (**Fig. 1**).

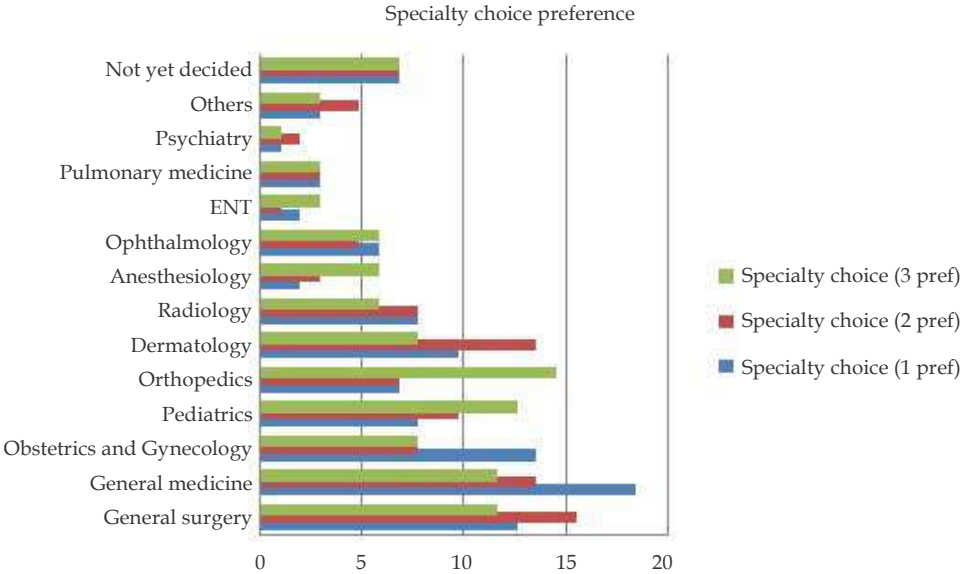

Fig. 1: Specialty choice preferences.

Among 59 males, 16 students (27.12%) choose general medicine as first career choice where as only 3 females (6.82%) choose general medicine as first career choice. 12 females (27.27%) choose obstetrics and gynecology as first career choice and 2 males (3.39%) choose it as first career choice (**Fig. 2**).

Overall only 2 (1.94%) students choose anesthesia as a first career choice. The most common reason for not choosing anesthesia as a career choice was lack of recognition by patients (21 students, 24.71%), followed by it being a dependant branch (16 students, 18.82%) (**Fig. 3**). The most common reason behind making a career choice was personal interest (20 students, 19.42%), followed by specialty recognition (13 students, 12.62%) as the second preferred reason behind making a career choice (**Fig. 4**). 32 students (31.02%) found that anesthesia as a specialty was interesting and life saving and 39 students (37.5%) found that anesthesia posting was interesting and important (**Table 1**).

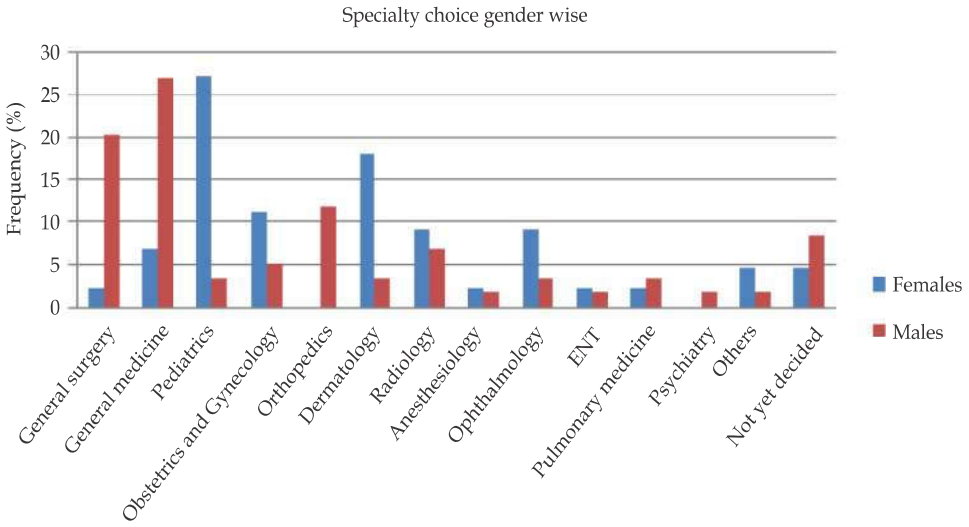

Fig. 2: Specialty choice gender wise.

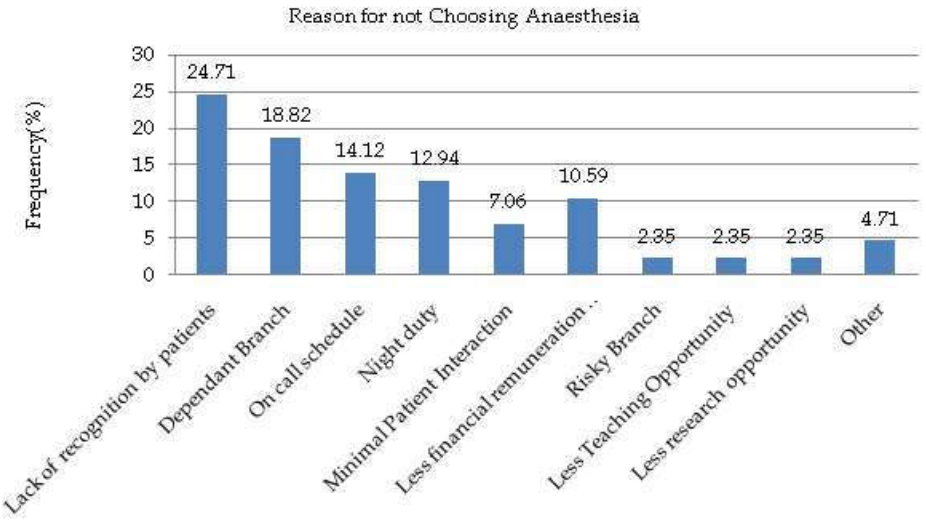

Fig. 3: Reason for not choosing anaesthesia as a career

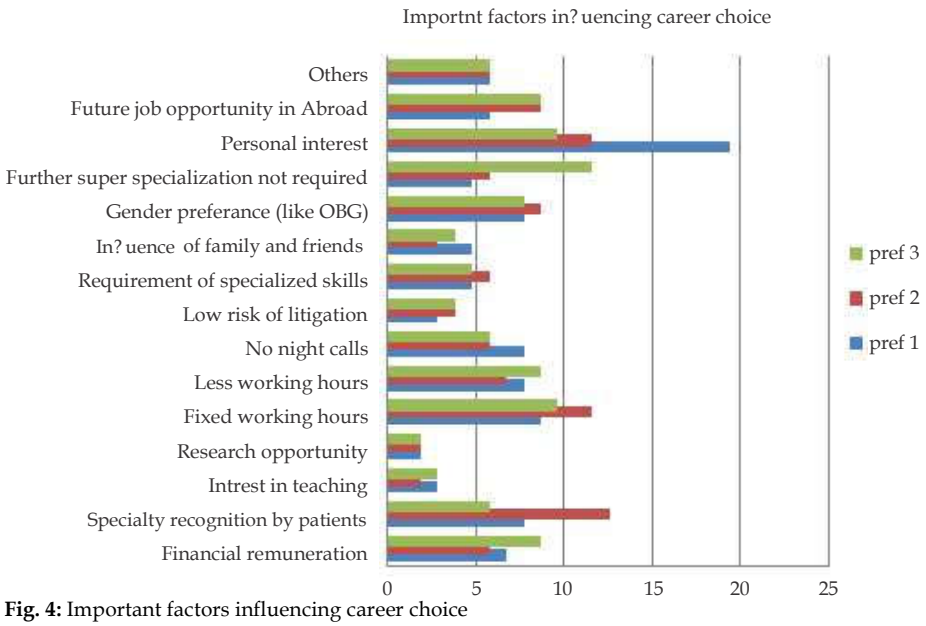

Fig. 4: Important factors influencing career choice

Table 1: Important factors influencing career choice

Anesthesia Specialty	Frequency	%
Interesting and life saving	32	30.8
Challenging and upcoming branch	20	19.2
Multi model	20	19.2
Too Stressful	15	14.4
Boring	8	7.7
No idea	9	8.7
Total	104	100

Anesthesia posting	Frequency	%
Interesting and important	39	37.5
Very informative	32	30.8
Too short	21	20.2
Boring	12	11.5
Total	104	100

Discussion

Anesthesiologists play a very important role in saving lives of critically ill patients by providing BLS, ACLS care, managing critical patients in ICU. This is in addition to its classic role of providing the best and safe conditions for the performance of surgery, by doing pre-anesthetic evaluation and optimising the patient's condition in order to reduce peri-operative morbidity and mortality, by providing peri-operative care.[4,5] About three decades ago, it was noted that the lack of interest in anesthesia as a specialty was because it was seen as unchallenging and lacking in primary patient care. This was attributed to lack of early exposure to the specialty.[4]

In our study we found that the most preferred specialty was general medicine followed by general surgery, orthopedics and obstetrics and gynecology. This was contrary to the other studies which showed general surgery was the most preferred specialty.[2] In our study, we found that there was an association between gender and the choice of future specialty.[6] Among 59 males, 16 students (27.12%) choose general medicine as first career choice where as only 3 females (6.82%) choose general medicine as first career choice. 12 females (27.27%) choose obstetrics and gynecology as first career choice and

2 males (3.39%) choose it as first career choice.[7,2] The students cannot practice independently and hence do not have hands on experience out of their hospital setting, hence the surroundings in which the students do their undergraduate studies influence their speciality choices.[7] Traditionally in our country OBG has evolved as a female dominant branch and medicine as a male dominant branch. Patient acceptance of a female gynecologist is more and this is one of the reasons for less number of males choosing OBG as their preferred specialty.[8]

In our research, among 103 students only 2 (2.08%) choose anesthesia as their first preferred specialty choice. Number of students choosing anesthesia as a second and third preference was more. This was consistent with studies conducted by Khan *et al.*[9] On questioning the reason for not choosing anesthesia, we found that the most common reason was lack of recognition by the patients followed by it being a dependant branch. This may be because, in developing countries like ours, there is lack of awareness among patients about anesthesia.[10] Whereas in developed countries the general public is more aware of anesthesia and anesthesiologists.

The most common reason behind choosing a specialty among the undergraduate medical students was personal interest in the specialty and this was consistent with findings in study conducted by Khan *et al.*[9] but was in contrast to the study conducted by Dikici *et al.*[11] The second factor influencing career choice was specialty recognition by patients. The duration of exposure of undergraduate students to a particular specialty varies with different institutes.[4] This varied exposure and also lack of provision of adequate aids such as mannequin are all contributory factors to the problem of limited or non-interest in anesthesia.[4, 12] This has resulted in the diminishing of medical students' clinical skills such as basic airway management, acute, and chronic pain management, and basic life support.

In our study, we found that 31.02% students thought anesthesia as a career was important and life saving and 37.5% students thought anesthesia as a posting was important and interesting.

Limitations

The limitation of our study was that it was a single institute study. Compulsory Rotatory Internship may change the specialty preference of the students and this may not be exact representation of the career choice that will be made following their graduation.

Conclusion

In our study, we have found that the most preferred career choice was general medicine and the most common reason behind making the career choice was personal interest. We need to emphasise on the positive aspects of anesthesiology like surging trends towards intensivists and pain specialists apart from the traditional subspecialties like cardiac anesthesia, neuro anesthesia, obstetric anesthesia, pediatric anesthesia, bariatric anesthesia and regional anesthesia to create interest regarding the specialty. Provision of adequate aids like mannequins and conducting BLS, ALS training, simulations and workshops at undergraduate level will also create interest in the anesthesia specialty.

Support: Nil

Conflicts of interest: Nil

Permissions: Nil

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Assessment of Knowledge and Attitute Towards Labor Analgesia among Pregnant Woman in MNR Medical College and Hospital

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Abstract

Introduction: Pain during labor is one of the major determinants of women's child birth experience. Epidural labor analgesia is the gold standard method now-a-days, with no harmful effects to the neonate but, beneficial effects has been observed. High acceptance rate of labor analgesia is observed in Developed countries, therefore, their data focuses on overall birth experience. *Materials and Methods:* Descriptive study was carried out on 120 expectant mothers attending the antenatal OPD of MNR Medical College and Hospital, Hyderabad over a period of 6 months. After taking informed consent 120 expectant mothers were selected by convenience sampling technique. Knowledge was assessed using structured questionnaire. Attitude was assessed using 3 point Likert scale consisted of 20 statements. *Results:* Majority of expectant mothers, 62 (52%) belongs to age-group of 28–31 years, 38 (32%) in age-group of 24–27 years, 10 (8%) in age-group of 20–23 years and other 10 (8%) in age-group of 32–35 years. Gravida distribution of expectant mothers, 66 (55%) had gravida one, 46 (38%) had gravida second and few 8 (7%) had gravida three. *Conclusion:* Most of expectant mothers had average level of knowledge but majority of had positive attitude. Most of the Indian parturient still suffer from the agony of labor pains due to lack of awareness, lack of availability or knowledge of availability of labor analgesia service. The awareness level needs to be improved.

Keywords: Labor pain; Epidural labor analgesia; Pregnant women.

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Introduction

Labor pain is one of the major determinants of women's childbirth experience. Epidural labor analgesia is the gold standard method,[1,2] with no evidence of harm to the neonate[3,4] but, beneficial effects has been observed.[5,6] Developed countries have high acceptance rate of labor analgesia,[7] therefore, their data focuses on overall birth experience.[8] In India, some information has been already documented to benefit the pregnant women about the use of analgesia in delivery. The very fact that, childbirth can be achieved without pain may seem absurd to many.[9] Culture, up bringing and ethnicity can influence the attitude towards pain.[10] Maternal request for pain relief suffices the indication for labor analgesia according to American Society of Anesthesiologists.[11]

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Women who received labor analgesia were highly satisfied with experience of childbirth.[12] This survey, assessed the awareness and acceptance about labor analgesia among antenatal women and attempted to point out the reasons for impediment for not receiving analgesia.[13]

Materials and Methods

This study was carried out on 120 expectant mothers attending the antenatal OPD of MNR Medical College and Hospital, Hyderabad over a *period of 6 months*. Informed consent was taken and 120 expectant mothers were selected by convenience sampling technique. Knowledge was assessed using structured questionnaire. Attitude was assessed using 3 point Likert scale consisted of 20 statements.

Inclusion Criteria

Expectant mothers who were in third trimester of pregnancy attending antenatal OPD of MNR Medical College and Hospital, Hyderabad, Telangana. Statistical analysis was done using Stata 11 software. Chi square test was used to assess statistical significance. A p - value < 0.05 was considered significant.

Results

Majority of expectant mothers, 62 (52%) belonged to age group of *28–31 years*, 38 (32%) in age group of *24–27 years*, 10 (8%) in age-group of *20–23 years* and other 10 (8%) in age-group of *32–35 years*. Distribution of expectant mothers according to gravida, 66 (55%) subjects had gravida one, 46 (38%) had gravida second and few 8 (7%) had gravida three (Fig. 1).

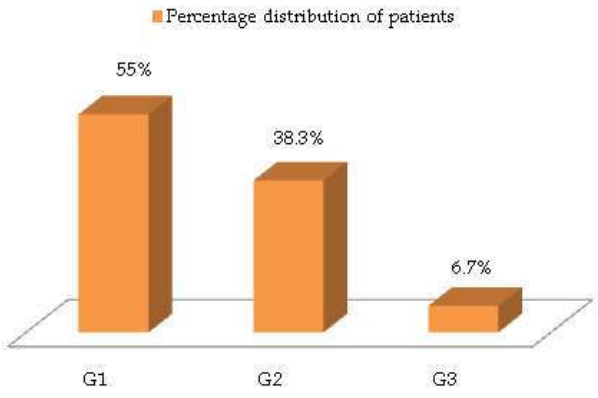

Fig. 1: Percentage distribution of patients according to Gravida

Figure 2 shows that 56 (46.7%) expectant mothers had below average level of knowledge, 42 (35%) had average level of knowledge and 22 (18.3%) had good level of knowledge regarding epidural analgesia. 96.7% had positive attitude and only 3.3 % had negative attitude towards epidural analgesia.

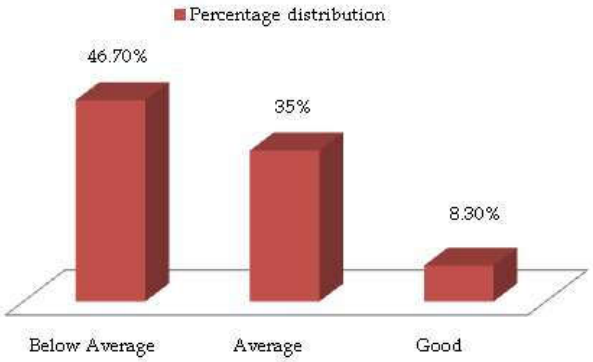

Fig. 2: Reveals the percentage distribution of expectant mothers as per their level of knowledge regarding epidural analgesia

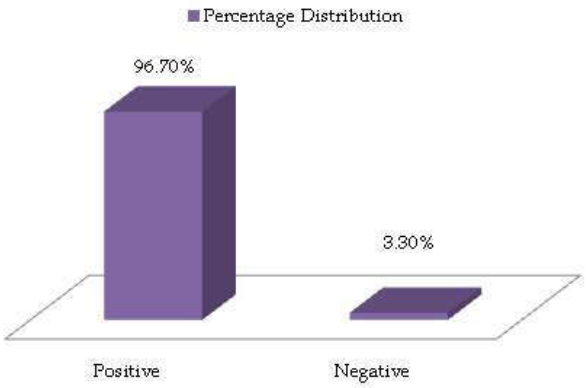

Fig. 3: Reveals that 96.70% had positive attitude *i.e.,* showed willingness to opt epidural analgesia and only 3.30% had negative attitude towards epidural analgesia.

The correlation was statistically tested (r = 0.609) and found to be significant (p - = 0.001). There was moderate positive correlation between knowledge with attitude. Hence, it can be concluded that there was positive effect of knowledge on attitude regarding epidural analgesia among expectant mothers. There was significant association of knowledge and attitude with education, occupation, habitat, previous knowledge regarding epidural analgesia, period of gestations at (p < 0.05) (Fig. 3).

Discussion

In the present study, knowledge and attitude regarding epidural analgesia among expectant mothers was assessed. The findings revealed that out of 120 expectant mothers, 56 (46.7%) expectant mothers had below average, 42 (35%) had average

and 22 (18.3%) had good level of knowledge regarding epidural analgesia. Similar study conducted by Kapadia Shital, Parmar Kartikeya, Solanki Nilesh and Patadia Kavita showed that 95% patients were totally unaware of the concept of labor analgesia.[6] 96.7% had positive attitude *i.e*., showed willingness to opt epidural analgesia during delivery and only 3.3% had negative attitude towards epidural analgesia. Similar study conducted by Shidhaye RV, Galande Mandar, Bangal VB and Smita Joshi results showed that 69% expressed their firm willingness to get delivered without labor pains and out of them 26% were very much eager for it, 25% showed inclination for painless labor by saying that they may like it, while only 6% were not at all interested.[5] Moderate positive correlation (r = 0.609) between knowledge and attitude. A similar study conducted by Hanem F Mohamed in Riyadh showed that there was a significant moderate correlation between parity and knowledge (r = 0.40, p = 0.000), income (r = 0.39, p = 0.001), education (r = 0.31, p = 0.000) and attitude (r = 0.31, 0.000).[4] There was significant association of knowledge and attitude with education, occupation, habitat, previous heard about epidural analgesia (p < 0.05). A study conducted by Minhas MR, Rehana, Afshan Gauhar, Raheel Hafsa in Karachi revealed that there was significant association of knowledge and attitude with level of education and attended antenatal classes.[7]

Conclusion

From this study. we are concluding that most of expectant mothers had average level of knowledge but majority of had positive attitude. Most of the Indian parturient still suffer from the agony of labor pains due to lack of awareness, lack of availability or knowledge of availability of labor analgesia service. The awareness levels in women needs to be improved. For this purpose, evidence based information on epidural analgesia should be provided during antenatal period to improve knowledge and attitude regarding epidural analgesia.

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Original Research Article

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Effect of Midazolam Pre-medication on Induction Dose of Propofol in Adult Patients in Elective Surgery

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Abstract

Introduction: The study based on that midazolam pre-medication reduces the induction dose and cost of propofol. *Aims:* To study effect of midazolam pre-medication on induction dose of propofol in adult patients. *Methods:* A prospective randomized, double blind control study was conducted. Total 60 patients (16–45 years) were divided into 2 groups. Group 1 received 0.05 mg/kg of Midazolam and Group 2 received Normal Saline. We compared the induction dose of propofol in both groups, taking loss of verbal contact as the end point. Additionally, changes in hemodynamic status like blood pressure and heart rate and induction time were studied and compared in both groups. *Results:* The dose of Propofol required to induce anesthesia in Midazolam group was 1.32 mg/kg and 2.27 mg/kg in the control group. The hemodynamic changes in Midazolam group compared to NS were non-significant. *Conclusion:* We recommend midazolam when used in combination with propofol reduces the dose of propofol and the time required for induction.

Keyword: Pre-medication; Midazolam; Induction; Propofol.

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Introduction

Pre-medication[1] refers to administration of drugs before induction and maintenance of anesthesia. It allays pre-operative fear, anxiety and tension. It facilitate rapid and smooth induction of anesthesia. It produces amnesia, sedation and analgesia. It also potentiates the anesthetic effects and hence may decrease the anesthetic requirement. Srivastava U *et al.*, and Amrein R *et al.* mentioned in their[2–4] that "Co-induction" is concurrent administration of two or more drugs that facilitate induction of anesthesia. Mckay AC *et al.* documented synergism in the study.[5,6]

Propofol is well-established as anesthetic inducing agent than thiopentone. Propofol and midazolam combination is commonly used for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression.[7–9]

Some recent studies have shown that administration of midazolam pre-medication reduces the intravenous induction dose of propofol. It reduces pain due to IV profopol and hence it reduces cost of the anesthesia.[10,11]

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Midazolam and propofol co-induction also lead to minimal hemodynamic changes. The technique of co-induction using two or more agents to induce anesthesia has been studied and synergism is reported between number of induction agents and midazolam.[7,9,12]

Objectives

To study the effects of midazolam pre-treatment on induction dose of propofol anesthesia in adult patients and also to study the hemodynamic changes with and without midazolam to propofol.

Meterials and Methods

A randomized control double blind study was conducted at the Department of Anesthesia at our institute during the period of *July 2010–July 2012*, after obtaining the approval of the institutional ethical committee. After obtaining written informed consent, total 60 patients belonging to both sex who were undergoing elective surgical procedures under general anesthesia, were enrolled.

Inclusion Criteria

ASA Grade 1 and 2 of aged between *15* and *45 years* who were scheduled for various elective surgical procedures under GA.

Exclusion Criteria

Difficult intubation, patients having pharyngeal pathology, cardiovascular and pulmonary disease, on medications like benzodiazepine, clonidine or beta blockers.

Pre-anesthetic evaluation was done in all patients a day prior to surgery. After detailed systemic evaluation, Patients who do not fall into our inclusion criteria were excluded. All patients were explained and after reassurance, informed consent was taken. All patients were kept nil by mouth for atleast *6 hours prior* to surgery. No pre-medication was given. Routine investigations like hemoglobin and urine examination were done in all patients. Blood sugar, Serum Creatinine and ECG were done in patients with age more than *40 years*. On arrival in the operation theatre, IV access was done with 18 G canula. ECG, pulse oximeter and NIBP were applied for monitoring. Patients were then assigned randomly into two groups namely: Group 1 (Midazolam + Propofol) and Group 2 (Saline + Propofol), according to the sealed envelope method by the anesthetic team not participating in the study but the researcher and the patient were unaware of their group. Either of the study drugs as priming were administered IV (Group 1- *0.05 mg/kg* of Midazolam, Group 2- normal saline) according to the randomization by the team, after pre-oxygenation for *3 minutes*, the study drugs was given IV diluted in *10 ml* of normal saline over a period of *10 seconds*. After *90 seconds*, anesthesia was induced by inj propofol *10 mg/ml* in a *20 ml* syringe at rate of *1 ml/second*, keeping continous verbal contact with the patient till loss of verbal contact and the total amount of propofol given was noted. Following this regular anesthesia was given with oxygen, nitrous oxide and inhalational anesthetic agent with or without muscle relaxant as per the needs of the procedure. Parameters assessed were induction time, dose of propofol, hypotension (Occurence of blood pressure < *90 mmHg* systolic), bradycardia (Incidence of pulse rate < *60 min*) and pain on injection of propofol. Statistical Analysis was done with SPSS and data was expressed as mean (standard deviation) for continous variables and proportion for qualitative variables. Student's *t*-test was used to test the statistical significance for quantitative variables and chi-square or fisher exact test for qualitative variables. $p < 0.05$ was considered statistically significant.

Results

The average age of the total patients were *35.45 years* ranging from *15 to 45 years*. In the group 1, the mean age was *35.9 years*, in group 2 it was *35 years*. Out of the 60 cases, 31 were males and 29 females. There were 11 male and 19 female patients in group 1, 20 male and 10 female patients in group 2. The mean weight of patients was *60.2 kg* ranging from *40 to 85 kg*. In the group 1, the mean weight was *60.73 kg*, in group 2 it was *59.20 kg*. The majority of the patients in all the groups were ASA Gr 1 (90%) however, 6 (10%) were in ASA Gr 2 of both gruop. The average requirement of Propofol varied significantly between the groups ($p < 0.001$), with mean *80.33 mg* in Group 1 and *134.66 mg* in Group 2 Mean Time required for induction in Group 1 was *31.5 seconds* and in Group 2 was *54.5 seconds* ($p < 0.001$). Hypotension noted after induction was 26.7% in Group 1 (midazolam + propofol) and 13.3% in Group 2 (NS + propofol) while 10% in Group 2 of patients only had bradycardia. Both findings were non-significant. Pain at the time of induction was 3.3% of patients in Group 1 and 36.7% in Group 2. So 96.7% in Group 1 and 63.3%

in Group 2 patients didn't have complaint of pain (χ^2 -10.41 and $p < 0.01$) showed in (**Tables 1–5)**.

Table 1: Gender distribution of the patients

Sex	Group 1 (%)	Group 2 (%)
Male	11 (36.6%)	20 (66.7%)
Female	19 (63.7%)	10 (33.3%)
Total	30 (100%)	30 (100%)

Table 2: Age and weight of the patient

Parameter	Group	Mean	SD*	t-Value	Probability
Age	1	35.90	7.685	0.463	0.645
	2	35	7.353		
Weight	1	60.73	11.307	0.628	0.532
	2	59.20	7.122		

*SD: Standard deviation.

Table 3: Induction dose of propofol

Group (*n*)	Mean Dose	SD*	*p* - Value
Group 1 (30)	80.33	28.61	< 0.001
Group 2 (30)	134.66	24.03	

*SD – Standard deviation.

Table 4: Induction time of propofol

Group (*n*)	Mean	SD*	
Group 1 (30)	31.5	12.26	*p* - Value < 0.001
Group 2 (30)	54.5	14.70	*t*-Value 6.581

*SD – Standard deviation

Table 5: Hemodynemic changes

Parameter		Group 1 (%)	Group 2 (%)
Hypotension	Present	8 (26.7%)	4 (13.3%)
	Absent	22 (73.3%)	26 (86.7%)
Bradycardia	Present	0 (0%)	3 (10%)
	Absent	30 (100%)	27 (90%)
Pain	Present	1 (3.3%)	11 (33.3%)
	Absent	29 (96.7%)	19 (66.7%)
Sedation	Present	1 (3.3 %)	0 (0%)
	Absent	29 (96.7%)	30 (100%)

Discussion

Propofol is a popular intravenous agent used to induce for general anesthesia, with a property to suppresses the upper airway reflexes adequately apart from producing a rapid induction. When used as a sole agent, children require a larger dose of propofol for insertion of laryngeal mask airway than adult.[7,13] This large dose needed for induction may be associated with hemodynamical and respiratory effect like hypotension, bradycardia, apnea or hypoventilation. It is currently considered 'gold standard'[14,15] for laryngeal mask insertion. Predosing with Midazolam is a reliable and effective method of reducing Propofol requirement. This study was undertaken to see the effectiveness of midazolam pre-medication on induction dose of propofol in adult patients. In our study, induction dose, induction time, hypotesion, bradycardia and pain were compared between both groups. In our study, mean induction dose was *80.33 mg* in Group 1 while *134.66 mg* in Group 2 ($p < 0.001$) when loss of response to verbal command, loss of eye lash reflex and loss of consciousness was taken as end point of induction.[10] Same observed in Shahin Jamil *et al.* study[16], that midazolam pre-medication is effective in reducing the induction dose of propofol and also the adverse effects due to higher induction dose of propofol. It also decreased the incidence of apnoea, but no clear benefits in terms of ease of LMA insertion and cardiovascular stability. Shahin Jamil *et al.* conducted a study on 60 ASA 1 and 2 patients, aged *15–45 years* for various surgical procedures with 30 patients in each group ($n = 30$). Group A (study group) received *0.05 mg/kg* midazolam while Group B (control) had saline as a pre-medicantion intravenously, followed by Fentanyl *1 mg/kg* after *90 seconds* of pre-medication. All patients were induced with propofol (*1.5 mg/kg*) *90 seconds* after fentanyl bolus. Our study can be compared with another study conducted by Kumar A *et al.* 17 who observed that there was 27.48% reduction in the induction dose of Propofol by applying priming principle. In his study[17] both the control group and the Propofol priming group received Midazolam (*0.05 mg/kg*) as a pre-medication and Fentanyl *15 minutes* prior to the induction. In study of Oliver H G Wilder-Smith[18] which was a controlled, randomized, double blind prospective study of 24 patients, who received either midazolam *0.05 mg/kg* or saline placebo as IV pre-medication *20 minutes* prior to induction, concluded midazolam pre-medication reduces the induction dose of propofol without affecting hemodynamics. Anderson L *et al.*, Short TG *et al.*, McClune S *et al.*, used midazolam and propofol combination for inducing patients and concluded in their study that midazolam and propofol shows synergistic interactions when midazolam used in sub-anesthetic doses and reduces the dose of propofol required for induction via a synergistic action.[4,5,6,7,9] In various studies like Driver IK *et al.*[19], Jones Na *et al.*[20], Gill PS *et al.*[21], Cressey DM[22], Martlew RA *et al.*[23] observed that use of midazolam reduces the induction dose of propofol and also acts synergistically.

We also found significant induction time of propofol. Mean induction time of Group 1 was

31.5 seconds and that of Group 2 was *54.5 seconds*. Our findings are comparable with study of Yushi U Adachi, Kazuhiko Watanable *et al*.[24], McKay AC.[5]

Bradycardia noticed only in 3 patients (10%) of Group 2 and none in Group 1 which was not significant. Our findings agrees with Goel S *et al*.[25], Djaiani G *et al*.[26] and Whitwan *et al*.[27], who used midazolam as co-induction agent along with propofol, noticed bradycardia which was non-significant. Though hypotension observed at the time of induction was higher in Group 1 (26.7%) than in Group 2 (13.3%) but it was not significant. This observation can be compared with observations of Djaiani G *et al*.[26], Anderson *et al*.[4], Jones Na *et al*.[20], Short TG *et al*.[7], Reinhart DJ *et al*.[28] found no significant difference in hypotension observed in their studies when midazolam and propofol are ued as co-induction agent.

Pain observed at the time of induction was 3.3% in Group 1 and 36.7% in Group 2 which was a significant ($p < 0.01$). Less pain was observed in patients who received midazolam before propofol, in study of Gill PS *et al*.[21], Edomwonyi N *et al*.[11], Leena Jalota *et al*.[10]

Conclusion

This study shows that Midazolam if used as a co-inductant, significantly reduces the induction dose and induction time of Propofol anesthesia. It also reduces the pain caused by intravenous propofol. It did not produce signifant hemodynamic instability or any undue delay in recovery. So we can recommend midazolam as a co-inducting agent and it also reduces the cost of propofol required for induction which is beneficial for our patients in a developing country.

Key Massage

Midazolam pre-medication reduces the induction dose and time for propofol.

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Conflicting interest: None stated.

Competing Interest: None stated.

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Original Research Article

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Ketamine as an Adjunct with Bupivacaine in USG Guided Paravertebral Analgesia for Modified Radical Mastectomy

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Abstract

Background: Adjuvants like fentanyl and clonidine have found to prolong the duration of analgesia when used along with local anesthetic in the paravertebral space for breast surgery. This study was planned to study the effect of addition of ketamine to bupivacaine for paravertebral block on intra-operative and post-operative analgesia in patient undergoing modified radical mastectomy under general anesthesia. *Materials and Methods:* This prospective, randomized, controlled double blind study was conducted in 60 women of ASA grade I–III age between 18 to 70 years who underwent modified radical mastectomy. Group A consisted of 30 patients receiving PVB with 0.3 ml/kg of 0.25% bupivacaine and 1 ml normal saline prior to GA and Group B consisted of 30 patients receiving PVB with 0.5 mg/kg ketamine along with 0.3 ml/kg of 0.25% bupivacaine in normal saline prior to GA. Intra-operative supplemental fentanyl consumption, hemodynamic parameter, pain score and post-operative morphine consumption were compared. *Results:* The mean intra-operative fentanyl consumption requirement in group A was 21.95 ± 21.58 µg, and 12.83 ± 19.93 µg in group B. (p = 0.828) 60% of the patients in group A did not require any analgesic supplementation which was comparable to that in group B (63.33%). First requirement of rescue analgesia in post-operative period was after 3.63 ± 2.55 hr in group A and 3.13 ± 2.84 hr in group B, (p = 0.480). The mean VAS values in both the groups were statistically comparable at rest and as well as on movement. (p > 0.05). *Conclusion:* The present study, showed that the addition of ketamine to bupivacaine did not improve the efficacy or duration of paravertebral analgesia in the post-operative and intra-operative period in patients undergoing modified radical mastectomy.

Keywords: Paravertebral block; Analgesia; Ketamine; Bupivacaine; Modified radical mastectomy.

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Introduction

Surgery in form of either lumpectomy or modified radical mastectomy with axillary node dissection, in combination with chemotherapy or radiotherapy remains the treatment of choice for breast cancer. Modified Radical Mastectomy (MRM) includes removal of the entire breast and axillary dissection, in which levels I and II of axillary lymph nodes are removed. Breast surgery is frequently associated with nausea, vomiting, pain and pain restricted movement.

Pain, according to definition endorsed by the International Association for the Study of Pain

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(IASP), is "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of such damage.[1] Post-operative pain managed in adequately, is documented to have several pathophysiological as well as economic implications, *e.g*., increased morbidity, duration of hospital stay and cost of medical care.

A wide variety of analgesic technique like local anesthetic infilteration, paravertebral and neuroxial analgesia, anti-convulsant, anti-neuropathic analgesic and NMDA (*N*-Methyl *D*-Aspartate) antagonist, apart from opioids based technique are employed for managing post-operative surgical pain following breast surgery. It is increasingly recognized that complex chronic pain syndrome may develop months to years later, if this acute post-operative pain is left untreated or undertreated.[2]

Paravertebral Block (PVB) for MRM was first described in April 1994 by Greegrass *et al*. He adapted the block for use in breast surgery, after surgeons asked for a way to prevent the intense side effects caused by general anesthesia (GA) precluding ambulatory surgery.[3] The technique used was modified by Eason and Wyatts' technique, which was simple to administered.[4] Before Eason and Wyatts described and standardized the technique, various other techniques were used by different authors.

PVB given prior to induction of GA, for breast surgery is known to provide improved intra-operative and post-operative analgesia, decreased incidence of nausea and vomiting, reduced surgical stress response and improved patient satisfaction. Therefore, Thoracic Paravertebral Block (TPVB) is the technique of injecting local anesthetic adjacent to the thoracic vertebra close to where the spinal nerve emerges from the intervertebral foramen. This result in ipsilateral somatic and sympathetic nerve blockade in multiple contiguous dermatomes above and below the injection site.[5]

Adjuvants like fentanyl and clonidine have already been used along with local anesthetic in the paravertebral space for breast surgery and have found to prolong the duration of analgesia.[6] The addition of ketamine to a local anesthetic or other analgesic in peripheral or neuroaxial anesthesia and analgesia improve or prolong pain relief.[7,8] Hence, this study was planned to study the effect of addition of ketamine to bupivacaine for paravertebral block on intra-operative and post-operative analgesia in patient undergoing modified radical mastectomy under general anesthesia.

Materials and Methods

This prospective, randomized, controlled double blind study was conducted in the Department of Anesthesiology and Intensive Care Unit at SN Medical College, Jodhpur. 60 women of ASA Grade I–III age between *18* and *70 years* who underwent modified radical mastectomy were included in study only after approval from Institution Ethical Committee and written informed consent from each patient were taken. Patients with local sepsis at site of block, severe chest wall deformity, coagulopathy or patient receiving any anticoagulants (platelet < 1,00,000), INR > 1.5, known hypersensitivity to amide type of local anesthetics, pregnancy, breast feeding and severe obesity BMI > *35 kg/m*^{2} were excluded from the study. The patients selected for the study were allocated to either group A or B using computer generated list of random permutations in double blind manner:

Group A: Consisted of patients receiving PVB with bupivacaine prior to GA. (*0.3 ml/kg* of 0.25% bupivacaine and *1 ml* normal saline).

Group B: Consisted of patients receiving PVB with bupivacaine with ketamine prior to GA (*0.5 mg/kg* ketamine along with *0.3 ml/kg* of 0.25% bupivacaine in normal saline).

The test solution was prepared by a fellow anesthesiologist who was not involved in the study so as to double blind the study. All the selected patients underwent a routine pre-anesthetic assessment, including explanation to the patient on post-operative pain assessment scale through visual analog scale (VAS). All the patients included in the study were premedicated with oral alprazolam *0.25 mg* two hours before the procedure. All of them were properly explained regarding the procedure of giving paravertebral block and were pre-loaded with *10–15 ml/kg* ringer lactate after I.V. line established with 18 G cannula on opposite hand. Baseline parameters including pulse rate, Non-invasive Blood Pressure (NIBP), oxygen saturation (SpO_2) and Respiratory Rate (RR) were recorded before starting PVB and before induction. The paravertebral block was performed prior to induction of general anesthesia.

All the patients received general anesthesia without testing the sensory level attained by TPVB. All patients premedicated with ondansetron *4 mg* and glycopyrrolate *0.2 mg*, then patients were induced with propofol (*1.5–2.5 mg/kg*, I.V.). Muscle relaxation was provided with vecuronium bromide after confirming adequacy of ventilation after loss of consciousness with propofol and the airway

was secured with appropriate size of endotraheal tube. The anesthesia was maintained with oxygen, isoflurane and vecuronium bromide. The $EtCO_2$ was maintained between *35–40 mm Hg*. Supplemental analgesia was provided with fentanyl *(0.5 µg/kg*) on the basis of rise in heart rate or systolic blood pressure by more than 20% of the base values for more than *5 minutes* (inadequate PVB was suspected). No other analgesia was administered intra-operatively. The number of doses and the total amount of supplement analgesia with fentanyl intra operatively was recorded for comparison between the two groups. Mephentermine *6 mg* was given in I.V. incremental dose to treat hypotension.

Continuous monitoring of HR, NIBP, SpO_2 and $EtCO_2$ were done in the intra-operative period and these were recorded every *15 minutes*. By end of surgery vecuronium effect was antagonized by I.V. Neostigmine *50 µg/kg* (max. *5 mg*) with glycopyrrolate *5 µg/kg*. After emergence patients were transferred to recovery room for a *2 hour* observation period. Analgesia in recovery room was provided by morphine *1 mg* I.V. as rescue medication, if needed, every *10 minutes* (a maxi. limit of *20 mg* in *4 hours*) until pain VAS score was ≤ 3. Time to first using the morphine was recorded and total dose of morphine was also calculated. HR, NIBP, SpO_2, RR and VAS score were also recorded at 0, 2, 6, 12 and 24 hours after the surgery. Ondansetron (*4 mg* I.V.) was given *8 hourly* as needed. Any psychomimetic changes (defined by agitation, hallucination or vivid dream) were also reported.

Data was recorded in 'Microsoft excel 2007' format and analyzed using SPSS version 15.0'. Continuous variable (age, weight, intra-operative supplemental fentanyl consumption, duration of surgery, hemodynamic parameter, respiratory rate, PONV scores, pain score and post- operative morphine consumption) were compared and analyze using student "*t*" test. Qualitative data (presence or absence of side effects and rescue anti-emetic drugs use) were analyzed using the chi-square test or Fischer's test, whichever applicable. A *p* - value less than 0.05 was considered significant for all parameters.

Results

Demographic data of all the patients in both the groups were found comparable ($p > 0.05$). The mean age of the patients in group A was *51.03 ± 13.81 years* compared to 54.4 ± 5.67 in group B. This difference was statistically not significant ($p = 0.757$) (**Table 1**).

The fentanyl consumption was found between *0 and 75 µg* in group A, *0 and 70 µg* in group B. The mean intra-operative fentanyl consumption requirement in group A was *21.95 ± 21.58 µg*, while in group B it was *12.83 ± 19.93 µg*. This difference was statistically non-significant.

($p = 0.828$) 60% of the patients in group A did not require any analgesic supplementation which was comparable to that in group B, where 63.33% of the patients did not require any supplementation of fentanyl (**Table 1**).

First requirement of rescue analgesia in post-operative period was after *3.63 ± 2.55 hr* and *3.13 ± 2.84 hr* in group A and B respectively which was statistically non-significant. ($p = 0.480$) 17 (28.33%) out of 60 patients consumed more than *30 mg* of morphine in *24 hours*. Among these 8 were in group A and 9 patients from group B. The cumulative consumption of morphine in both the group was comparable. ($p > 0.05$) (**Table 1**).

The mean VAS values in both the groups were statistically comparable at rest and as well as on movement (coughing) ($p > 0.05$) (**Table 2**).

Intra-operative and post-operative heart rate, systolic blood pressure and diastolic blood pressure, SpO_2 and $EtCO_2$ were recorded at *0, 2, 6, 12* and *24 hours* post-operatively. The recording at all interval were found comparable in both

Table 1: Demographic and other characteristics of both the groups

	Group A (Mean ± SD)	Group B (Mean ± SD)	*p* - value*
Age (*yrs*)	51.03 ± 13.81	49.93 ± 13.67	0.757
Weight (*kg*)	54.4 ± 5.67	54.53 ± 7.83	0.104
ASA grade	1.77 ± 0.49	1.83 ± 0.637	0.658
Mean duration of surgery (minutes)	103.83 ± 16.15	108.33 ± 14.47	0.293
Intra-operative fentanyl consumption (*ug*)	21.95 ± 21.58	12.83 ± 19.93	0.828
Time of first requirement of rescue analgesia-morphine (*hr*)	3.63 ± 2.55	3.13 ± 2.84	0.480
24 consumption of rescue analgesia-morphine (*mg*)	24.06 ± 7.239	25. 27 ± 5.965	0.486

**p* - value (> 0.05) non-significant for all parameters.

Table 2: Post-operative VAS score at rest and on movement

Time of measurement (hr)	VAS score at rest (Mean ± SD)			VAS score on movement (Mean ± SD)		
	Group A	Group B	p - value*	Group A	Group B	p - value*
0	2.58 ± 1.27	2.97 ± 1.36	0.244	5.33 ± 1.32	5.90 ± 1.03	0.069
2	2.32 ± 0.61	2.48 ± 0.68	0.321	4.43 ± 0.68	4.90 ± 0.76	0.075
6	1.90 ± 0.50	2.06 ± 0.45	0.181	3.47 ± 0.57	3.77 ± 0.63	0.057
12	1.77 ± 0.50	2.03 ± 0.65	0.813	2.87 ± 0.57	3.07 ± 0.67	0.227
24	1.83 ± 0.40	1.93 ± 0.75	0.527	2.56 ± 0.63	2.83 ± 0.79	0.153

*p - value (> 0.05) non-significant at all intervals at rest as well as on movement.

the groups. This difference was not statistically significant. (p > 0.05) There was no incidence of urinary retention, pruritus, pneumothorax or respiratory depression in any of the group. 7 out of the 10 patient with Post-operative Nausea-vomiting (PONV) in group A required anti-emetic; while 5 out of 8 patients with PONV required rescue anti-emetic in group B.

Discussion

Pain is a critical focus of patient care. Substantial improvement in knowledge of mechanisms and treatment of pain has been outcome of extensive research, but unfortunately, this has not been translated into appropriate patient satisfaction. Post-operative pain is still inadequately relieved. This study focusing on alleviating the acute post-operative pain following MRM by performing PVB and prolonging this duration of analgesia by addition of an adjuvant in form of Ketamine along with local anesthetics in PVB.

The demographic parameters of the patients included in both the groups were comparable in this study. The duration of surgery in the both groups was also comparable. The variation in duration of surgery among these patients could be attributed to the varied skill and expertise of the operative surgeon and intra-operative finding.

In present study, paravertebral block was combined with GA. For the same reason 0.25% Bupivacaine was used instead of 0.5%. Burlacu *et al.* too had combined single shot paravertebral block (0.25% bupivacaine) with GA. Paravertebral space is not as isolated structure but communicates with paravertebral space above and below.[9] Thus, in this study USG guided technique was performed instead of blind technique, this was to ensure an increased probability of successful block. The block was performed just prior to induction of anesthesia. The onset of block quoted in various studies varies from *10–20 minutes*.[10] The sensory block however, could not be checked as general anesthesia was induced immediately following block.

Single injection PVB at T_4 level was found to be a suitable alternative to GA in women undergoing breast surgery by Pusch *et al*.[11] The multisegmental spread of single injection paravertebral block was confirmed by Saito *et al.* in a voluntary study.[12] Burlacu *et al.* also confirmed the efficacy of single injection paravertebral block at T_4 level.[6]

One of ways in which the efficacy of block can be assessed is checking for sensory loss for pin prick, which could not be assessed in this study as GA was immediately induced after performing block. But as a surrogate to checking of sensory loss, intra-operative analgesic requirement was used. The mean fentanyl consumption in groups A and B were comparable. The difference was statistically non-significant. About 60 % in group A and 63.33 % in group B patients did not require fentanyl intra-operatively. Thus, block was fully effective in these patients. In the rest of the patients the block was either partially effective or failed.

Moore *et al.* described that there is a tendency for caudal spread of the drugs when injected into paravertebral space.[13] This explain inadequate block at T_1 dermatome in this study, as the block was performed at T_4 level. In this study, sitting posture was used for performing block, which could not influenced spread of drugs in TPVS.

The VAS scores at rest in the immediate post-operative period were comparable in the both groups. This might be because of analgesia provided by block and fentanyl supplementation provided intra-operatively, which continued with PCA morphine in the immediate post-operative periods in the both groups. This is similar to observation made in other studies which showed low pain scores in immediate post-operative period.[6] The subsequent VAS scores on movement were also comparable in both the groups. This was because of the participants had already been instructed to call nurse to inject morphine in order to maintain their

pain score less than 4. VAS score greater than 3 was considered the cut off for inadequate analgesia based on several studies reviewed by Dolin *et al*.[14]

The efficacy of block was also assessed with morphine consumption in post-operative period in the both groups. First requirement of rescue analgesia in post-operative period were similar in both the groups and difference was statistically insignificant. Similar result was found by Singh *et al*.[15] In this study, mean total consumption of morphine in group A and group B were also similar. This difference was statistically non-significant. This could be attributed to the efficacy of block being similar in the both groups.

In this study, we did not find any prolongation in duration of block. This variable effect of ketamine probably can be explained from different site of injection. In human study, showing effective analgesia, ketamine with local anesthetics was administered with incisional infiltration of subcutaneously.[10,16] The analgesic effect thus may have been consequences of a pure local effects of ketamine at the level of surgical trauma where a wound inflammation occurs.[17,18]

The dose of ketamine used (*0.5 mg/kg*), might have been absorbed quickly in systemic circulation and any local anesthetic effects could have been masked especially with the long acting used Bupivacaine local anesthetic. This also might have happened in Lee *et al.* study as they injected their study solution in the interscalene area which is vessels rich.[19] The relative high incidence of ketamine related psychomimetic adverse effects in this study may support this explanation. In present study, no psychomimetic effect were seen any of the groups. This can be explained as the good analgesia enhancing effect and lack of psychomimetic effect of ketamine when given in the epidural or caudal route where the systemic absorption is slow. The present study hypothesized that ketamine either act at the nerves as they emerges from intervertebral foramen or diffuse into epidural space and act on spinal cord. However, results obtained in this study do not substantiate either of these hypotheses.

In this study, there was no episode of intra-operative hypotension in either of two groups. This could be due to intravascular absorption of ketamine from paravertebral space. The absorption from paravertebral space is quite high, ranked next only to that from the intercostal nerve block.[20] Ketamine stimulates cardiovascular system and usually associated with increases in HR and BP.[21] The post-operative hemodynamic parameters were also comparable between both the groups. This could be because of maintaining lower pain scores in both the groups.

The PVB technique is associated with certain complication like pleural puncture, pneumothorax, epidural or subarachnoid placement, intravascular injection and horner's syndrome.[22] No incidence of pneumothorax was observed in this study. This might be attributed to the enhanced safety associated with USG Guided technique and less number of cases. Several others studies on PVB for breast surgery show similar results.[23,24]

Epidural or subarachnoid spread has also been reported with PVB. Weltz *et al.* have reported 2 cases of epidural spread of local anesthetics in a study of thirty patients using PVB as the sole anesthesia for inguinal hernia repair.[25] Klein *et al.* also reported one incidence of epidural spread without hemodynamic in stability out of 24 patients receiving PVB for inguinal herniorrhaphy.[26] The present study also, did not have any case of epidural spread.

Incidence of failed block could not be estimated from this study as we did not assess loss of sensation following PVB placement and general anesthesia was induced in most patients immediately after PVB. Failure rate after PVB in adults varies from 6.1–10.7%.[23] This reflects technically difficulty in identifying paravertebral space. The above quoted figures are failure rate following nerve stimulator guided technique. Several others studies on PVB for breast surgery quote similar failure rates.

The mean PONV scores immediately post-operative period were comparable in the both groups. In this study, similar PONV scores and incidence between the two groups could be because of combining PVB with GA. This observation has again confirmed by other studies.[11,25,27]

Conclusion

The present study showed that the addition of ketamine to bupivacaine did not improve the efficacy or duration of paravertebral analgesia in the post operative and intra-operative period in patients undergoing modified radical mastectomy.

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An Observational Study of Small Dose Propofol and Midazolam as Co-induction Agents to Propofol

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Abstract

Introduction: Propofol has become the most widely used I.V. hypnotic agent. It provides rapid induction but the major disadvantages are cardiovascular and respiratory dysfunction hence, the concept of "Auto-co-induction" and "Co-induction" has come forward. The current study, has been designed to evaluate reduction in induction doses of propofol and alteration in peri-intubation hemodynamic in propofol auto-co-induction and midazolam propofol co-induction groups along with propofol group. *Materials and Methods:* The present study, is a prospective, observational and non-interventional study, which includes 75 patients of age between 20 and 50 years with ASA grade I. All the patients were divided into three groups and each group have 25 patients Group I (PP), Group II (MP), Group III (P). Two minutes prior to induction agent Group I received 0.5 mg/kg propofol, Group II received 0.05 mg/kg midazolam. Induction dose of propofol and hemodynamic parameters during various interval were measured. *Results:* Propofol induction dose in Group I,II,III, was 74.4 mg, 66.36 mg and 136.4 mg respectively which was statically significant ($p < 0.05$) when group Iand II compare with group III. Hemodynamic stability in peri-intubation period was better in group I that mean auto-co-induction. *Conclusion:* We conclude that midazolam co-induction and propofol auto-co-induction significantly reduce the induction dose of propofol, propofol auto-co-induction provides better hemodynamic stability in peri-intubation period. The priming appears to be cost effective by significantly reducing the total dose of propofol required and no significant adverse intra-operative or post-operative effects were observed in all groups.

Keywords: Auto-co-induction; Co-induction; Midazolam; Propofol.

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Introduction

An important landmark in the development of anesthesia has been the discovery of an intravenous induction agents. Propofol was introduced in the 1970s and it has become the most widely used I.V. hypnotic agent. It provides rapid induction but the major disadvantages are cardiovascular and respiratory dysfunction hence, the concept of "Auto-co-induction" and "Co-induction" has come forward.

"Auto-co-induction"[1,2] is a technique of giving a pre-calculated dose of induction agent prior to giving the full dose of same induction agent;

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this technique is also known as "the priming technique".[3]

"Co-induction"[4,5] is defined as the concurrent administration of two or more drugs that facilitate induction of anesthesia documenting *synergies*[6] and to decrease the dose requirement of the induction agent to make the quality of anesthesia better with improvement in hemodynamic stability. The commonest co-induction agent to propofol has been midazolam.[7,8]

The current study, has been designed to evaluate reduction in induction doses of propofol and alteration in peri-intubation hemodynamic in propofol auto-co-induction and midazolam propofol co-induction groups along with propofol group.

Materials and Methods

The present study, was a prospective, observational and non-interventional study, which included 75 patients of age between *20* and *50 years* with ASA grade I, posted for various elective surgeries under general anesthesia to Choithram Hospital and Research Center from *March 2015* to *November 2015*.

Approval from the Ethics Committee and Scientific Review Committee and a written informed consent for participation in the study was taken. Pre-operative clinical assessment of the patients was done and on the day of surgery patients were pre-medicated with pre-anesthetic agents. All the patients were divided into three groups in a consecutive manner; accordingly each group has 25 patients:

Group I (*n* = 25): had received propofol *0.5 mg/kg* + propofol as induction agent.

Group II (*n* = 25): had received midazolam *0.05 mg/kg* + propofol as induction agent.

Group III (*n* = 25): had received propofol alone as induction agent.

Baseline measurement of blood pressure, pulse rate and arterial O_2 saturation were taken before placement of IV cannula. Patients were pre-oxygenated with 100% oxygen (*8 L/min*) using face mask and Bains circuit for three minutes, and then were administered fentanyl. *1 mcg/kg* followed by co-induction agent which was *0.05 mg/kg* midazolam (Group II) or *0.5 mg/kg* propofol (Group I).

Two minutes after the co-induction agent injection, each patient received propofol at the rate of *30 mg* every *10 seconds*. Eyelash reflex was checked. If there was no response, propofol injection was stopped, and face mask applied firmly. Any complication during this period, *i.e.*, apnea, vomiting, laryngospasm, involuntary movements, coughing, was noted.

The anesthesia continued according to the standard practice of intubation after rocuronium *1 mg/kg*. Anesthesia was maintained on O_2/N_2O (35%, 65%); inhalational agent, *i.e.*, isoflurane and injection rocuronium. No stimuli were applied during the *10-minutes* post-intubation period.

The following parameters were recorded:

1. Induction dose of propofol.
2. Blood pressure [(systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP)] and heart rate (HR) measured at the following intervals and recorded in a customized performa:

- Baseline (before placement of I.V. cannula);
- Immediately after co-induction agent;
- Immediately after induction agent;
- Immediately after intubation;
- Then at *5 minutes* and *10 minutes.*

The comparison between the three was done using one-way ANOVA. The post-hoc tukey test was applied to find out the statistical difference between the groups.

Results

In the present study, total 75 patients aged between *20 and 50 years* were included and as per study design, they were consecutively divided into 3 groups. Mean age and weight were compared among 3 groups. No statistically significant difference was found among three groups as the *f* - value is 1.39 and *p* - value is > 0.05 (**Table 1**).

Table 1: Sociodemographic details

	Mean age	Mean weight
Group I	29.92 ± 7.60	59.28 ± 8.61
Group II	31.88 ± 9.04	57.52 ± 7.48
Group III	28.36 ± 5.27	58.80 ± 6.63

Mean propofol induction dose were compared among 3 groups. Statistically significant difference was found among three groups as the *f* - value

is 185.28 and p - value is < 0.05. As per post-hoc tukey test the p - value for Group I and Group II pair was found to be > 0.05, which is statistically insignificant and for Group III-II and Group III-I pairs p - value was found to be < 0.05 *i.e.*, statistically significant (**Table 2**). Various hemodynamic parameters at different intervals for all the 3 groups were compared (**Table 3**). At baseline heart rate, systolic and diastolic blood pressure values show statistically insignificant difference as p - value was > 0.05 (**Table 3**).

Table 2: Mean propofol induction dose used in the three groups

	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)
Induction dose	74.40 ± 13.49	66.36 ± 10.66	136.40 ± 17.29

After administration of priming dose (post-priming) of propofol and midazolam in group I and II respectively, the mean heart rate shows statistically insignificant results (p - > 0.05). Same results were obtained in post-hoc tukey test for group I and group II (**Table 3**).

We observed similar results as heart rate for post-priming systolic blood pressure for group I and group II *i.e.*, statistically insignificant values in both ANOVA and post-hoc tukey test (p > 0.05) (**Table 3**).

Whereas post-priming diastolic blood pressure for Group I and group II shows statistically significant results (p - value < 0.05). For pair also the post-hoc tukey test was found to be statistically significant (< 0.05) (**Table 3**).

Again the post-induction heart rate and systolic blood pressure showed statistically insignificant difference between the three groups (p > 0.05). Similarly values of diastolic blood pressure in all three groups showed statistically significant results (f = 10.50 and p < 0.05) (**Table 3**).

For post-induction systolic and diastolic blood pressure post-hoc tukey test showed the p - value < 0.05 for group III-I and Group III and II pair. Thus, there was statistically significant difference between pair, but for group I and II pair p - value was found to be > 0.05 (insignificant) (**Table 3**).

The post intubation heart rate values showed similar variations among all three groups as same as post-induction values *i.e.*, statistically insignificant (p > 0.05). Whereas post- intubation systolic and diastolic blood pressure showed p - value < 0.05 means statistically significant (**Table 3**).

In post-hock tukey test for post-intubation systolic blood pressure showed statistically significant difference among all the three pairs of group, whereas for post-intubation diastolic blood pressure p - value was found to be significant for pair group I–II and group III-II but not for pair group I–III. Heart rate after *5 minutes* shows no significant difference between the three groups (p > 0.05), whereas after *10 minutes* it shows significant variation in values (**Table 3**).

In post-hoc tukey test after *5 minutes* heart rate shows no significant difference among all the three pairs, whereas for after *10 minutes* heart rate statistically significant variation was found between group I and III and group II and III. *5 minutes* and *10 minutes* systolic blood pressure shows statistically significant variation (p - value < 0.05) in all the three groups. Post-hock tukey test shows significant value for pair group I and II and group II and III for systolic blood pressure after 5 and 10 minutes (**Table 3**).

Diastolic blood pressure after 5 and 10 minutes shows statistically significant variation (p - value < 0.05) among all the three groups. Post-hock tukey test shows significant value after *5 minutes* diastolic blood pressure for pair group I–II and I–III, whereas after *10 minutes* significant value was found for pair group I–II and II–III (**Table 3**).

Table 3: HR, SBP and DBP values for all the three groups

	HR			SBP			DBP		
Time Point	**I**	**II**	**III**	**I**	**II**	**III**	**I**	**II**	**III**
Baseline	86.84 ± 11.16	86.28 ± 13.32	84.88 ± 12.70	124.00 ± 10.35	123.64 ± 6.78	125.72 ± 10.50	77.72 ± 7.39	80.12 ± 6.83	80.68 ± 6.93
Post– priming	83.20 ± 10.36	80.68 ± 12.00		117.88 ± 8.88	119.80 ± 4.84		73.12 ± 5.55	77.04 ± 6.43	
Post- induction	77.56 ± 9.12	75.44 ± 8.76	74.48 ± 11.17	108.48 ± 8.97	110.32 ± 7.34	98.04 ± 9.44	67.48 ± 5.50	70.72 ± 6.46	62.56 ± 6.96
Post- intubation	87.84 ± 8.38	88.64 ± 8.31	91.36 ± 12.25	118.16 ± 8.08	135.08 ± 8.48	126.80 ± 12.88	74.36 ± 6.33	94.28 ± 5.73	78.84 ± 8.91
After 5 *min*	80.68 ± 8.65	80.44 ± 7.51	84.60 ± 18.55	112.08 ± 9.32	125.24 ± 8.66	108.80 ± 6.73	69.64 ± 6.16	78.88 ± 5.29	75.88 ± 4.36
After 10 *min*	76.60 ± 8.59	75.96 ± 6.86	82.52 ± 9.99	108.40 ± 8.93	115.24 ± 7.85	104.08 ± 6.37	66.64 ± 5.88	75.48 ± 4.91	64.92 ± 4.28

Discussion

Propofol though a wonderful I.V. anesthetic induction agent with many advantages also has some side effects like hypotension, bradycardia, apnea, etc. which are dose dependent, so a reduction in the induction dose would thereby reduce the associated side-effects, the most important being the effect on cardiovascular system leading to hemodynamic instability.

We found that co-induction agents were effective in reducing the induction dose of propofol considerably compared to propofol alone as an induction agent. Dose reduction following midazolam is probably due to synergistic interaction between the two drugs. Synergism has been reported between agents with known functional link in the central nervous system *viz*. midazolam and propofol acting on a common receptor site, the GABA receptors. The dose reduction in the propofol auto-co-induction group was probably due to 'priming effect'. The small dose of propofol prior to induction dose caused sedation and anxiolysis, thus allowing induction of anesthesia with lower doses of propofol.

In our study, we have observed a significant reduction in the induction dose requirement of propofol in group I (45.45%) as compared to group III which was statistically significant. Our results were similar to Kataria *et al*. (2010)[9] and Amatya *et al*. (2014)[10] they found reduction in dose of induction 31.88% and 27.48% respectively. Group II shows significant reduction in induction dose requirement (51.34%) as compare to group III. Our results were similar to Kataria *et al.* (2010)[9] they found reduction in dose of induction 45.37%. Whereas in Djaiani *et al.* (1999)1 significant reduction of the total induction dose of propofol in both group ($p < 0.001$) were observed.

After induction with propofol heart rate decreased in all the three groups which were 10.68% in group I (PP), 12.56% in group II (MP) and 12.25% in group III (P). Result were not statistically significant between group I (PP) – group III (P) and group II (MP) – group III (P). Our results were similar to Anderson *et al.* (1998)[4] and Srivastava *et al*.[5] they have reported fall in heart rate during induction in all three groups.

After intubation heart rate increased in all the three groups and was statistically not significant. Maximum increase in heart rate from baseline seen in group III (P) (7.63%) and least rise in group I (PP) (1.15%). Our results were similar to Katariar *et al*.[9], they have reported rise in heart rate after intubation least in propofol-propofol group, and maximum rise in propofol group.

After induction systolic blood pressure decreased in all three groups which were 12.51%, 10.77% and 22.01% in Group I, Group II and Group III respectively. Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Kumar *et al*.[2]

After intubation, systolic blood pressure increased in all three groups. Maximum rise in systolic blood pressure was observed in Group II (9.25%). Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Amatya A *et al*.[10] and Kataria *et al.* (2010).[9]

After induction, diastolic blood pressure decreased in all three groups which was 13.17%, 11.73% and 22.45% in Group I (PP), Group II (MP) and Group III (P) respectively. Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Amatya A *et al*[10] and Kumar *et al*.[2]

After intubation, diastolic blood pressure increased in all groups. Maximum rise in diastolic blood pressure from baseline was observed in Group II MP (17.67%). Results were statistically significant on comparing Group II (MP)–III (P) but on comparing Group I–III statistically insignificant results were obtained and our results were similar to Kataria *et al*.[9] they have reported that after intubation, maximum increase in diastolic pressure was observed in group II (MP) propofol.

Conclusion

From above findings we conclude that midazolam co-induction and propofol auto-co-induction significantly reduce the induction dose of propofol. Propofol auto-co-induction provides better hemodynamic stability in peri-intubation period. The priming appears to be cost effective by significantly reducing the total dose of propofol required and no significant adverse intra-operative or post-operative effects were observed in all groups.

Abbreviation

I.V. - Intra vascular

O_2 - Oxygen

N_2O - Nitrous oxide

SBP - Systolic blood pressure

DBP - Diastolic blood pressure

MAP - Mean arterial pressure

HR - Heart rate

PP - Propofol-propofol

MP - Midazolam-propofol

P - Propofol

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Original Research Article

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Effects of Dexmedetomidine Infusion on Hemodynamic Stress Response, Sedation and Post-operative Analgesic Requirement in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Dexmedetomidine is a selective α2 agonist with sedative, analgesic and sympatholytic properties and hence, it can be used as an anesthetic adjuvant. *Aims:* We aimed primarily to evaluate the effects of low dose Dexmedetomidine infusion on hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. The secondary aims were to observe the effects on sedation levels, post-operative analgesia requirements and occurrence of adverse effects. *Methods:* Ninety patients of American Society of Anesthesiologists [ASA] physical grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into three groups of 30 patients each as follows:

Group NS: [Saline group; n = 30] – Received 0.9% normal saline infusion;

Group DEX: 0.2-Patients received Dexmedetomidine infusion 0.2 mcg/kg/hr;

Group DEX: 0.4-Patients received Dexmedetomidine infusion 0.4 mcg/kg/hr.

Infusions were started 15 min before induction and continued till end of surgery. Parameters noted were pulse rate, mean arterial pressure, post-operative sedation and analgesia requirements. SPSS 15.0 version software was used for statistical analysis and Continuous data were analyzed by ANOVA test.

Results: In Group NS, significant hemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. In Dexmedetomidine groups, the hemodynamic response was significantly attenuated. The results, however, were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in Dexmedetomidine groups. No significant side effects were noted. *Conclusion:* Low dose Dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates hemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

Keywords: Dexmedetomidine; Hemodynamic stress response; Laparoscopic cholecystectomy.

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Introduction

The development of minimally invasive surgery has revolutionized the field of surgery. Laparoscopic cholecystectomy is one of the most commonly practiced surgeries for gall bladder diseases in the present era.

The physiological response to surgical stress

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and anesthesia is well documented. In the earlier review by Kehlet, the stress response to surgery is more than anesthesia drugs and technique. A wide number of anesthetic drugs have been used in clinical practice to modify the stress response to anesthesia and surgery. Laparoscopic surgery which involves insufflation with carbon dioxide produces undesirable responses like hypertension, tachycardia, and dysrhythmias.

Introduction of Dexmedetomidine which is highly specific and selective α2 adrenoceptor agonist has been tried in various studies to modify the stress response to surgery and to have a pleasant anesthetic outcome with minimal cardiovascular changes.

In present study, we have taken the pharmacological advantage of Dexmedetomidine to study the various cardiovascular parameters at different periods during the laparoscopic procedure.

Materials and Methods

Type of study: Prospective randomized controlled double blind clinical study.

Duration of study: Jan 2017 to June 2018.

The institutional ethical committee approved the study and written informed consent was obtained from all the patients before being included in the study.

Selection Criteria

Inclusion

90 ASA Grade I and II of *18 to 65 years* of age of either sex posted for laparoscopic cholecystectomy were included in this study.

Exclusion

Elderly, Diabetic patients, Patients with chronic Hypertension, Severe CARDIAC disease, Pregnant or Lactating women, Patients with a history of allergy to egg proteins and α2 agonists were excluded from the study.

The patients were randomly allocated to three groups - 30 Patients each, by envelope method as follows:

Group NS: [Saline group; n = 30] – Received 0.9% normal saline infusion;

Group DEX: 0.2-Patients received dexmedetomidine infusion *0.2 mcg/kg/hr*.

Group DEX: 0.4-Patients received dexmedetomidine infusion *0.4 mcg/kg/hr*.

A thorough pre-anesthetic evaluation was performed by taking history and clinical examination. In all patients age, weight, Systolic blood pressure, Diastolic blood pressure and Heart rate were recorded. All patients were investigated thoroughly to rule out cardiac, renal, hepatic and endocrine problems.

Infusion was prepared by taking dexmedetomidine *0.5 ml* containing *50 mcg* of the drug withdrawn in a *50 ml* syringe and was diluted up to *50 ml* with normal saline resulting in the final concentration of *1 mcg/ml*. Both normal saline and dexmedetomidine was given through schiller syringe infusion pump. According to the patient weight, the pump was set so as to deliver the targeted infusion rate.

On arrival in the operation theatre, monitors were attached, and baseline parameters such as heart rate, systemic arterial pressure, and oxygen saturation were noted down. Two intravenous lines were secured, one *20 guage* cannula in the right hand for the infusion and another *18 gauge* cannula in left hand for intravenous fluids and drug administration. *500 ml* of crystalloids [Ringer Lactate] was started.

Fifteen minutes after starting the drug infusion, pre-oxygenation was performed for *3 minutes*.

Patients were pre-medicated with Inj. ondansetron *2 mg* I.V.

Inj. Glycopyyrolate *0.2 mg* I.V.

Inj. Ranitidine hydrochloride *50 mg* I.V.

Inj. Fentanyl *1 mcg/kg* I.V.

Patients were induced with Inj. Propofol *2 mg/kg*. Endotracheal intubation was facilitated by succinylcholine *1.5 mg/kg*. Anesthesia was maintained with O_2:N_2O, sevoflurane 0.6 vol% and vecuronium bromide *0.1 mg/kg*. Intermittent positive pressure ventilation was continued by the mechanical ventilator to maintain end-tidal carbon dioxide between *35–40 mm of Hg* Pneumoperitoneum was created by insufflation of carbon dioxide at the rate of *2 liters/min*. Intra abdominal pressure was maintained at 12–14 *mm Hg* throughout the surgical procedure. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with nitroglycerine infusion.

Systemic arterial pressure including the systolic, diastolic and mean arterial pressure, heart rate, Saturation, End-tidal carbon dioxide and electrocardiography were recorded at the following points of time:

1. Before starting of infusion *15 minutes* after infusion
2. *1 minute* after induction
3. *1 minute* after intubation
4. *1 minute* after Pneumoperitoneum
5. *5 minutes* after Pneumoperitoneum
6. *12 minutes* after Pneumoperitoneum
7. *30 minutes* after Pneumoperitoneum
8. *45 minutes* after Pneumoperitoneum
9. *60 minutes* after pneumoperitoneum
10. *1 min* after the release of Pneumoperitoneum
11. *1 minute* after extubation

After completion of surgery patients were reversed with Glycopyrrolate *0.01 mg/kg* and Neostigmine *0.05 mg/kg*. After thorough suction patients extubated and shifted to the recovery room. Patients were observed for post-operative sedation level, time for first rescue analgesic [inj. Paracetamol *1gr*/I.V.], adverse effects.

Statistical Analysis

The sample size was decided in consultation with the statistician and was based on initial pilot study observations, indicating that approximately 23 patients should be included in each group in order to ensure a power of 0.80 for detecting clinically meaningful difference by 15% in heart rate and mean arterial blood pressure. Assuming a 5% dropout rate, the final sample was set at 30 patients in each group, which would permit a type1 alpha (a) error = 0.05, with a type 2 error of beta (β) = 0.2 and power of 0.8. the results obtained in the study were presented in a tabulated manner and analysed using Microsoft excel and SPSS 20 Software. The results of the present study between the three groups was compared statistically using Analysis of Variance (ANOVA) and Student "t "test. A p - value < 0.05 was taken as statistically significant.

Fig. 1: Used materials

Fig. 2: Inducing the drug

Results

All the three groups under study were comparable to each other with respect to age, sex, weight, ASA grading, duration of surgery and anesthesia (shown in **Table 1** and **Graph 1**). There was no significant

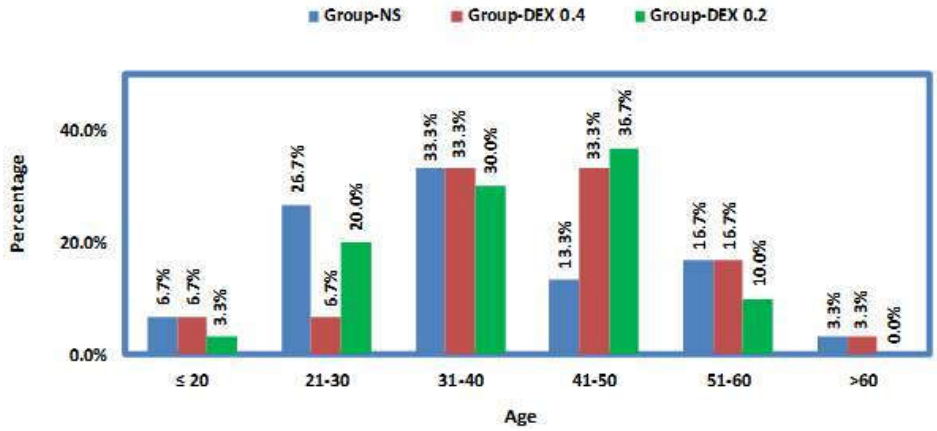
Table 1: Age distribution

Age	Group-NS		Group-DEX 0.4		Group-DEX 0.2	
	Count	%	Count	%	Count	%
≤ 20	2	6.7%	2	6.7%	1	3.3%
21–30	8	26.7%	2	6.7%	6	20.0%
31–40	10	33.3%	10	33.3%	9	30.0%
41–50	4	13.3%	10	33.3%	11	36.7%
51–60	5	16.7%	5	16.7%	3	10.0%
> 60	1	3.3%	1	3.3%	0	0.0%
Total	30	100.0%	30	100.0%	30	100.0%

p = 0.53

difference among the three groups in reference to the baseline PR and the MAP, shown as in **(Tables 2, 3)**.

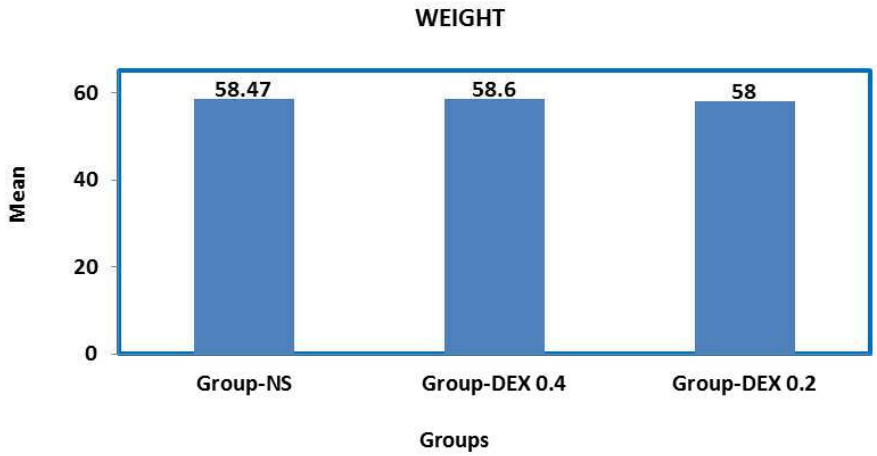
In both the Dexmedetomidine groups, after starting the infusion, the PR decreased highly significantly below the pre-infusion level. The MAP decreased significantly in Dex 0.2 group and highly significantly in Dex 0.4 group. No further significant changes were observed immediately after induction. After intubation and extubation, the PR and MAP increased significantly above the



Graph 1: Age distribution

Table 2: Showing according to weight

Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p*-value
	Mean	SD	Mean	SD	Mean	SD	
Weight	58.47	9.07	58.60	8.29	58.00	9.01	0.96

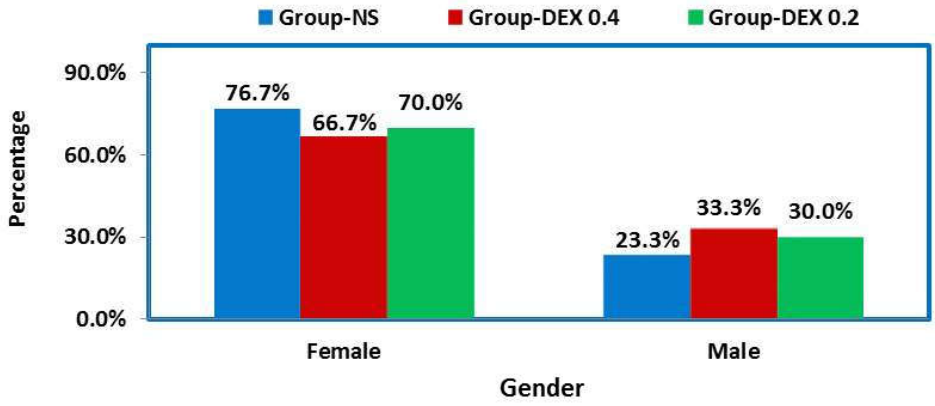


Graph 2: Showing according to weight

Table 3: Showing sex distribution

Sex	Group-NS		Group-DEX 0.4		Group-DEX 0.2	
	Count	%	Count	%	Count	%
Female	23	76.7%	20	66.7%	21	70.0%
Male	7	23.3%	10	33.3%	9	30.0%
Total	30	100.0%	30	100.0%	30	100.0%

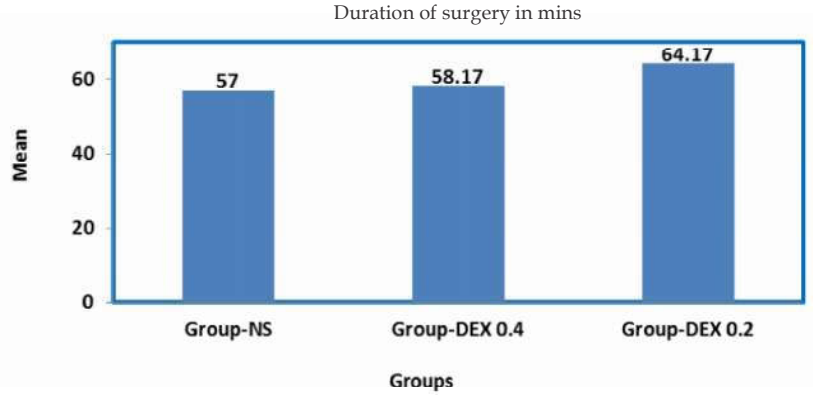
$p = 0.69$



Graph 3: Showing sex distribution

Table 4: Showing duration of surgery in minutes

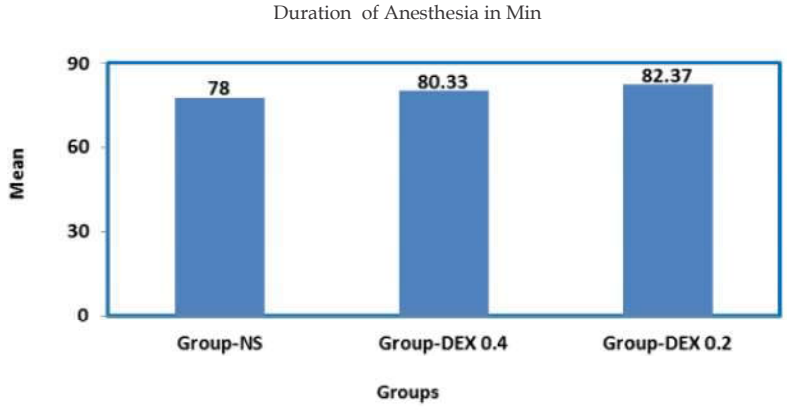
Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
Duration of surgery in mins.	57.00	13.56	58.17	11.48	64.17	13.90	.079



Graph 4: Showing duration of surgery in minutes

Table 5: Showing duration of anesthesia in minutes

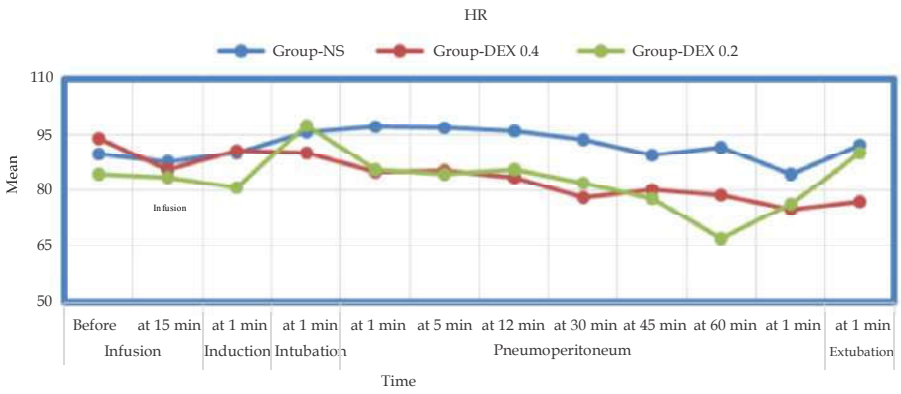
Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
Duration of anesthesia in mins.	78.00	16.06	80.33	9.55	82.37	12.97	.439



Graph 5: Showing duration of anesthesia in minutes

Table 6: Heart rate

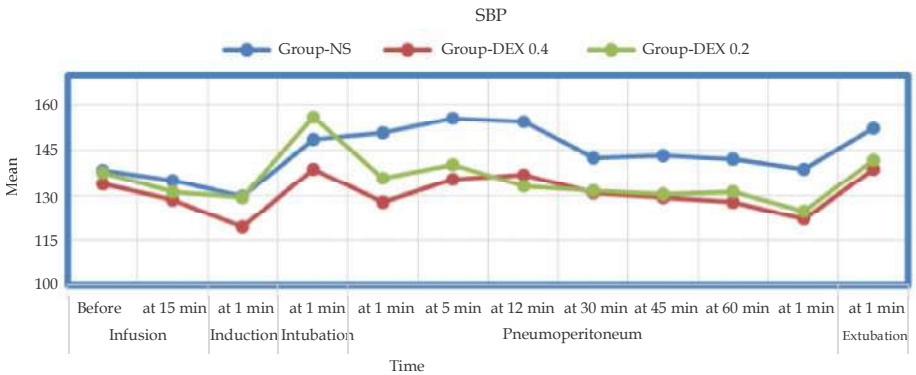
HR	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	89.70	12.54	94.00	18.50	84.27	11.37	.038
Infusion at 15 *min*	87.63	11.96	85.60	25.52	83.60	12.49	.681
Induction at 1 *min*	90.10	10.72	90.63	15.68	80.67	10.73	.004
Intubation at 1 *min*	95.73	10.95	90.13	20.68	97.37	11.42	.154
Pneumoperitoneum at 1 *min*	97.07	11.68	84.90	11.35	85.70	16.80	.001
Pneumoperitoneum at 5 *min*	96.97	12.70	85.33	11.66	84.50	18.70	.002
Pneumoperitoneum at 12 *min*	95.93	11.66	83.50	18.35	85.43	12.86	.003
Pneumoperitoneum at 30 *min*	93.63	13.22	78.11	11.72	81.96	14.25	< 0.001
Pneumoperitoneum at 45 *min*	89.38	11.75	80.21	12.55	77.80	17.54	.011
Pneumoperitoneum at 60 *min*	91.65	12.99	78.64	15.07	66.92	13.69	< 0.001
Pneumoperitoneum release at 1 *min*	84.47	8.62	74.73	11.24	76.28	13.68	.003
Extubation at 1 *min*	92.03	13.00	76.77	17.26	90.10	16.18	< 0.001



Graph 6: Heart rate

Table 7: Showing systolic blood pressure

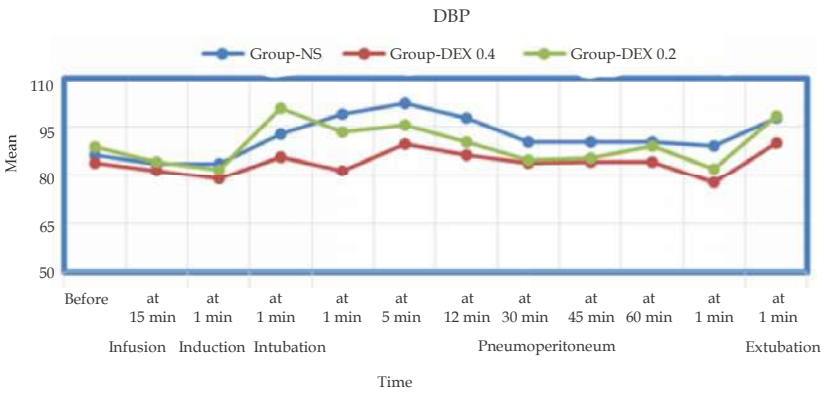
SBP	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	138.40	16.73	133.93	15.85	137.50	8.90	.443
Infusion at *15 min*	134.93	15.23	128.40	11.36	131.03	7.68	.105
Induction at *1 min*	129.87	17.83	119.60	25.32	129.27	10.71	.067
Intubation at *1 min*	148.57	14.42	138.60	12.68	156.03	18.72	< 0.001
Pneumoperitoneum at *1 min*	150.97	16.12	127.63	10.22	135.90	12.74	< 0.001
Pneumoperitoneum at *5 min*	155.93	13.68	135.27	14.42	140.40	11.28	< 0.001
Pneumoperitoneum at *12 min*	154.57	10.85	137.00	14.40	133.23	10.86	< 0.001
Pneumoperitoneum at *30 min*	142.47	14.70	131.00	14.04	131.43	13.92	.003
Pneumoperitoneum at *45 min*	143.46	7.41	129.42	7.68	130.56	9.53	< 0.001
Pneumoperitoneum at *60 min*	142.24	8.09	127.86	10.72	131.08	13.41	.001
Pneumoperitoneum release at *1 min*	138.77	8.24	122.30	10.65	124.90	9.31	< 0.001
Extubation at *1 min*	152.47	9.04	138.87	13.57	141.80	13.93	< 0.001



Graph 7: Showing systolic blood pressure

Table 8: Showing diastolic blood pressure

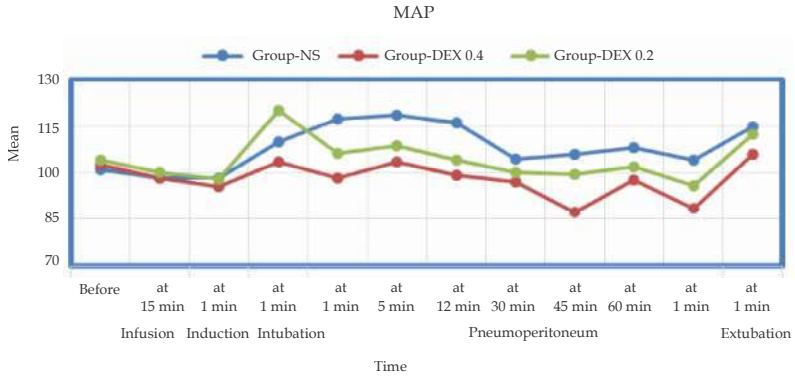
DBP	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
Before Infusion	86.37	9.18	84.00	10.42	88.73	6.09	.118
Infusion at *15 min*	83.50	7.84	81.47	8.25	84.27	8.82	.407
Induction at *1 min*	83.60	7.93	79.03	8.10	81.63	10.18	.137
Intubation at *1 min*	92.70	6.50	85.90	11.62	100.67	20.22	< 0.001
Pneumoperitoneum at *1 min*	99.03	12.31	81.40	8.21	93.53	11.90	< 0.001
Pneumoperitoneum at *5 min*	102.23	9.83	89.67	12.64	95.60	8.29	< 0.001
Pneumoperitoneum at *12 min*	97.67	7.04	86.43	13.21	90.23	8.47	< 0.001
Pneumoperitoneum at *30 min*	90.30	8.23	83.89	9.26	84.86	11.02	.026
Pneumoperitoneum at *45 min*	90.23	6.69	84.17	6.03	85.56	7.73	.006
Pneumoperitoneum at *60 min*	90.47	5.30	84.21	7.15	89.00	5.95	.022
Pneumoperitoneum release at *1 min*	89.20	6.70	77.93	6.32	82.07	7.65	< 0.001
Extubation at *1 min*	97.67	8.16	90.07	12.50	98.30	13.52	.012



Graph 8: Showing diastolic blood pressure

Table 9: Map

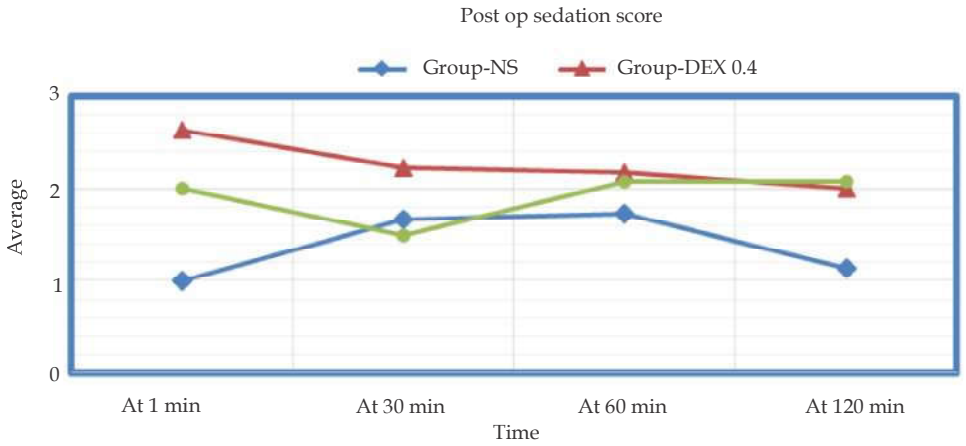
Map	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p*- value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	101.00	12.51	102.57	14.08	104.17	9.49	.604
Infusion at *15 min*	98.37	10.08	98.47	9.98	100.03	7.85	.742
Induction at *1 min*	98.20	8.79	95.60	8.94	97.97	11.10	.517
Intubation at *1 min*	109.90	7.34	103.43	12.46	120.03	20.38	< 0.001
Pneumoperitoneum at *1 min*	117.33	10.93	98.30	10.23	106.37	11.50	< 0.001
Pneumoperitoneum at *5 min*	118.43	12.90	103.57	17.00	108.80	10.10	< 0.001
Pneumoperitoneum at *12 min*	115.90	8.96	99.13	15.99	104.00	10.61	< 0.001
Pneumoperitoneum at *30 min*	104.37	10.93	97.07	13.18	100.07	11.88	.072
Pneumoperitoneum at *45 min*	105.96	7.70	87.38	19.50	99.44	7.15	< 0.001
Pneumoperitoneum at *60 min*	108.18	7.12	97.71	9.10	102.08	9.44	.005
Pneumoperitoneum release at *1 min*	104.03	7.68	88.47	9.90	95.80	8.63	< 0.001
Extubation at *1 min*	114.67	9.48	106.00	13.22	112.40	13.49	.020



Graph 9: Map

Table 10: Post-operative sedation score

Post-operative sedatio score	Group-NS		Group-DEX 0.4		Group-DEX 0.2		*p* - value
	Mean	SD	Mean	SD	Mean	SD	
At *1 min*	1.00	0.00	2.63	0.49	2.00	0.00	< 0.001
At *30 min*	1.67	0.48	2.23	0.43	1.50	0.51	< 0.001
At *60 min*	1.73	0.45	2.17	0.38	2.07	0.25	< 0.001
At *120 min*	1.13	0.35	2.00	0.00	2.07	0.25	< 0.001



Graph 10: Post-operative sedation score

pre-infusion level in Dex 0.2 group, though, this increase was less compared to increase in group NS [$p < 0.05$]. Unlike these changes in Dex 0.2 group, PR and MAP in Dex 0.4 group remained below pre-infusion level after intubation and extubation [$p < 0.05$ when compared with Dex 0.02]. Pneumoperitoneum did not produce a significant effect in both the Dex groups.

The post-operative means sedation scores were observed using Ramsay Sedation score (RSS) at *1 min*, *30 min*, *60 min*, *120 minutes*. When compared to Group NS patients sedation scores are more in dexmedetomidine groups. Group DEX 0.4 patients had better sedation than Group DEX 0.2. The patients were co-operative, oriented and tranquil all the time. In Group NS, less sedation score was observed initially; the later score was improved due to the early requirement of analgesia in this group (**Table 4**).

The mean Rescue analgesia time in Group NS patients was 21.50 ± *10.76 minutes*, in Group DEX 0.4 - *299.27 ± 86.64 minutes* and in Group DEX 0.2 - *172.00 ± 75.13 minutes*. When compared between three groups *p* - value was < 0.001 which was statistically significant (**Tables 5–10**).

Discussion

Laparoscopic procedures involve peritoneal insufflations with Carbon dioxide and create pneumoperitoneum. This induces intra-operative ventilatory and hemodynamic changes that complicate anesthetic management for laparoscopy.[1]

The hemodynamic variability due to laparoscopy is due to release of humoral factors, and potential mediators are catecholamines, prostaglandins, and vasopressin.[2] The reverse trendelenburg position required for surgery leads to diminished venous return and thereby further reduction in cardiac output.[3]

Dexmedetomidin offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability associated with the great advantage to avoid respiratory depression.[4,5] In particular, Dexmedetomidine can provide dose-dependent "co-operative sedation" that allows ready interaction with the patient.[6] Hence, we have decided to use Dexmedetomidine infusion for laparoscopic cholecystectomy 2 important issues that are noted in this study are Pharmacological actions of Dexmedetomidine and physiological

responses to surgery, anesthesia, and Laparoscopy. *a*2-Adrenoceptor agonists do not affect the synthesis, storage, or metabolism of neurotransmitters and do not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the *a*2-agonist effects with a specific *a*2-adrenoceptor antagonist. Therefore, they may have a role in anesthesia for patients who are at high risk of myocardial ischemia while undergoing major surgery.

The α2-receptors regulate the autonomic and cardiovascular systems. *a*2-receptors are located on blood vessels mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release.[7,8]

Manne *et al*. in a pilot study, they used low dose infusionsof dexmedetomidine without any bolus. Initially, they used dexmedetomidine *0.2 mcg/kg/h* infusion, it controlled the rise in PR and MAP after the creation of pneumoperitoneum, the control was not very effective at the time of endo tracheal intubation and extubation.

The Pulse Rate and Mean Arterial Pressure both increased above pre-infusion levels. Hence, they increased the dose to *0.4 mcg/kg/hr* infusion in our next two patients. The results were quite satisfactory with this dosing regime. PR and MAP were always below pre-infusion levels in Dex 0.4 group. We also studied few cases with Dex *0.6 mcg/kg/hr* dose but the hypotension was seen in a greater number of patients, and the sedation was more (RSS 4–5). Hence, they have taken three groups in their study, which were Group NS, Group Dex 0.2 and Group Dex 0.4. Their study confirmed the fact that critical incidences like laryngoscopy and intubation, pneumoperitoneum and extubation do significantly increase the Mean Arterial Pressure and Pulse Rate in patients undergoing laparoscopic cholecystectomyas seen in group NS. Dexmedetomidine attenuatesthis sympathoadrenal response and provides hemodynamic stability. The effective attenuation dose with minimum side effects noted in our study was *0.4 mcg/kg/hr* infusion.[9]

In present study, *0.2 & 0.4 mcg/kg/hr* were used as study dose and found to be effective which correlates with the above study.

The Pulse Rate and Mean Arterial Pressure both increased above pre-infusion levels *15 minutes* after infusion and after intubation in group DEX 0.2 group. But it controlled the rise in PR Bhattacharjee *et al.*[10] also observed no significant effect of Dexmedetomidine on response to verbal command and extubation time. Dexmedetomidine has been found to reduce the intra and post-operative requirement of opioids.[11–14] This effect is called as an Opioid-sparing effect. The time for first rescue analgesic is increased in dexmedetomidine groups. In our study, we observed two patients of DEX 0.2 group did not require any analgesia on the day of surgery.

Providing post-operative analgesia and comfort to the patient was also anesthetist concern only. With this consideration the drug which was used in present study helped with its analgesic property.

Group NS patients in present study, had pain post-operatively around 20–30 minutes after the surgery. In 2 patients of group NS were given injection Paracetamol *1 gr* intravenously immediately after surgery also.

Group DEX 0.2 patients have post-operatively analgesia siginificantly when compared to group DEX 0.4. Surprisingly two patients who received DEX *0.2 mcg/kg/hr* had no pain for *24 hours* and did not require any rescue analgesic. Three pateints of DEX 0.2 had pain immediately after extubation, so we have given injection Paracetamol I.V. for them in the recovery room.

Group DEX 0.4 patients were pain-free and very comfortable in the post-operative period. They have received rescue analgesia around *300 minutes* [*5 hours*] after surgery.

Adverse effects

No serious adverse effects were observed in this study.

In one patient endobronchial intubation occurred. Saturations were reduced, immediately endotracheal tube position adjusted and saturations became normal.

Limitations of the study

The limitations of the present study are inability to assess the depth of Anesthesia. Dexmedetomidine attenuates hemodynamic response, and it was very difficult to assess the depth of anesthesia. BIS monitoring and catecholamines estimation were not practical in cases studied.

Conclusion

Dexmedetomidine may provide an attractive alternative to anesthetic adjunctive agents now in use because of their anesthetic-sparing and

hemodynamic-stabilizing effects. Low dose Dexmedetomidine infusion given at the rate of *0.4 µgram/kg/hr* is quite effective for laparoscopic surgery. It provides better peri-operative hemodynamic stability than many agents now in use and may offer protection from ischemia due to the attenuated neuroendocrine response. The drug is to be given in infusion rather bolus to avoid complications like bradycardia and hypotension. Dexmedetomidine may have a role in anesthesia for patients who are at high risk of myocardial ischemia while undergoing laparoscopic surgery. Dexmedetomidine a new, more selective *a*2-adrenoceptor agonist may provide a new concept for the administration of peri-operative anesthesia and analgesia.

Abbreviations

ASA - American Society of Anesthesiologists

BP - Blood Pressure

BPM - Beats per minute

DBP - Diastolic Blood Pressure

$EtCO_2$ - End-tidal carbon dioxide concentration

G - Gauge

MAP - Mean Arterial Pressure

HR - Heart Rate

SBP - Systolic Blood Pressure

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Original Research Article

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Effectiveness of Dexmedetomidine to Reduce Bleeding During Tympanoplasty and Functional Endoscopic Sinus Surgery (FESS): An Interventional Study

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Abstract

Context: Bleeding during the nasal and middle ear surgeries can impair the visibility of the surgical field. Controlled hypotension is a technique used to bring down the Mean Arterial Pressure (MAP) and reduce the bleeding in the surgical field. *Aims:* To evaluate the effectiveness of dexmedetomidine, a selective α2-adrenoceptor agonist, on reducing the intra-operative bleeding and duration of surgery. *Settings and Designs:* Randomized, double blind, control study. *Materials and Methods:* We included sixty patients who were posted for tympanoplasty and FESS under general anesthesia and divided randomly to Group D where dexmedetomidine 1 µg/kg loading dose plus a maintenance of 0.5 to 0.8 µg/kg/hr and Group P in whom normal saline 1 ml/kg loading dose and 1 ml/kg/hr maintenance was administered. Heart rate and MAP was measured at 15,30,45,60 minutes and at extubation. Bleeding severity score and the duration of surgery were noted. Student t-test and chi-square test were used for data analysis, p - value < 0.05 was considered statistically significant. *Results:* The fall in heart rate, MAP was more in the Group D than in Group P and was significantstatistically (p < 0.05). Bleeding severity score was lower in the Group D than in Group P. (none of the patients had a score of 3 in Group D and in Group P 10 patients had a score of 3). The mean duration of surgery was also less in the Group D (55.55 min ± 2.34) when compared to Group P (68.39 min ± 4.38) which was statistically significant (p < 0.01). *Conclusion:* Dexmedetomidine infusion started as loading dose along with intra-operative maintenance results in a decrease in the MAP, reduced bleeding and shorter surgical duration.

Keywords: Bleeding severity score; Controlled hypotension; Dexmeditomidine; Placebo.

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Introduction

A blood less field is needed while performing Tympanoplasty and Functional endoscopic sinus surgery [FESS] in order to provide a better vision to the surgeon.[1–3] It is a challenge to the anesthesiologist to provide the same. The method of reducing the blood pressure in order to reduce the bleeding in the intra-opreative period and in turn improve the operative field visibility is called controlled hypotension.[4] Volatile anesthetic agents, sodium nitroprusside, nitroglycerine, beta blockers and calcium channel blockers are some of the drugs used to produce controlled hypotension.[5–7] Problems that can be seen with these drugs can be a delay in recovery when volatile anesthetics are used, drug resistance with vasodilators, cyanide toxicity and tachyphylaxis with nitroprusside.[8–10]

Selective α2 receptor agonist Dexmedetomidine has anti-hypertensive effect. It also has other

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properties like analgesia, sympatholysis and sedation without causing major respiratory depression. It has been used to suppress sympathetic response also. Opioid requirement is also decreased in addition to a reduction in stress responses to surgery and post-operative shivering.[11] Previous studies have concluded dexmeditomidine to be beneficial in tymoanoplasty and FESS. As dexmeditomidine was not used in our institution routinely we decided to conduct this study to know if it can effectively reduce bleeding in tymoanoplasty and FESS surgeries.

Materials and Methods

ASA class I and II patients sixty in number of both sex, in the age group of *18–40 years*, scheduled to undergo elective FESS and tympanoplasty under general anesthesia were selected for the study. Institutional ethical committee approval and written informed consent from the patients were obtained. Two groups, the dexmedetomidine group (D) and the placebo group (P) were done and patients were allotted randomly in to one of them. Patients with comorbid diseases coming under ASA II and ASA III physical status, pregnant females, patients with bleeding disorders, patients having Sinus Bradycardia, Heart Block, Conduction defects, Ischemic Heart Diseases (IHD)/Rheumatic Heart Disease, Chronic Renal Diseases with deranged renal parameters and hypotension pre-operatively were not included in the study. This study was done in the Operation theatre with facilities for Induced Hypotension and Resuscitation. Patients were examined in the pre-operative period and laboratory investigations, Electrocardiogram (ECG) and chest *X*-ray were ordered. Patients were kept nil by mouth for eight hours.

On shifting to Operation theatre, an 18G/20G I.V. canula secured and dextrose normal saline infusion was started. Monitors were connected to record non-invasive blood pressure, Pulse rate, ECG, O_2 saturation and end-tidal carbon dioxide.

Heart rate, Blood Pressure both Systolic and Diastolic and MAP before induction were recorded. Bolus dose of dexmedetomidine *1 µg/kg* over *10 mins* in an infusion of *100 ml* normal saline was started in Group (D), and normal saline *100 ml* infusion in Group (P) at a rate of *1 ml/kg/hr* via an extension of *25 cms* connected to the canula with the maintenance fluid. Injection glycopyrrolate *0.2 mg* was given before induction of anesthesia and injection fentanyl *1.5 µg/kg* given for analgesia. Pre-oxygenation with 100% oxygen was done for *3 minutes*, induction of anesthesia done using injection Propofol *2 mg/kg*, endotracheal intubation facilitated with injection succinylcholine *1.5 mg/kg*, and intubated with a appropriate sized tube. Maintenance of anesthesia was done with nitrous oxide and oxygen 65:35 ratio along with 0.4%–1% isoflurane and vecuronium *0.05 mg/kg* used for intra-operative muscle relaxation. During intra-operative period a maintenance dose of dexmedetomidine at *0.5–0.8 µg/kg/hr* was used in Group D and the infusion rate was reduced if the MAP went below *60 mm* of *Hg* or heart rate below 50 beats per minute and Normal saline infusion *1 ml/kg/hr* was continued in Group (P). The infusions were stopped *20 minutes* before the end of surgery. Heart rate and blood pressure was noted before any intervention, at *15,30,45,60 minutes* after drug administration, and at the time of extubation for statistical analysis but a continuous monitoring of heart rate and blood pressure every five minutes was done during surgery. Atropine *0.6 mg* was given if the heart rate was 50 beats per minute. Ephedrine *5 mg* increments was used to correct MAP if it went below *60 mm Hg*. Opinion of the surgeon regarding the operative field and intra-operative bleeding was assessed using the Bleeding severity score obtained by the following questionnaire and graded accordingly. We modified the score used by Fromme *et al.*[2]

0-virtually blood less field without any bleeding. 1-A mild Bleeding that was not a surgical nuisance. 2-Moderate bleeding causing a surgical nuisance not interfering with accurate dissection. 3-Moderate bleeding that compromised the surgical dissection moderately. 4-A severe bleeding but controllable and interfering significantly with surgical dissection. 5-Massive bleeding which could not be controlled and made dissection impossible.

The anesthesiologist recording the parameters and the surgeon were both unaware of the drug administered. Ondansetron *4 mg* intravenous was administered *30 min* prior to end of surgery for anti-emesis. Duration of surgery in minutes was recorded. Glycopyrrolate *0.02 mg/kg* and Neostigmine *0.05 mg/kg* was used for reversing the residual neuromuscular block after the completion of surgery and patients were shifted to the recovery area and were shifed from the recovery on achieving Aldrette score of 9. Purposive sampling technique was used to calculate sample size with the confidence interval (1-α) at 95% and power of study (1-β) at 80%. Data was entered in Microsoft excel, statistics were calculated using stata 14.1 software. Numerical data was calculated from mean and standard deviation, categorical variables using

percentage. Student *t*-test was used for numerical data and chi-square test for categorical data, *p* – value < 0.05 was considered statistically significant.

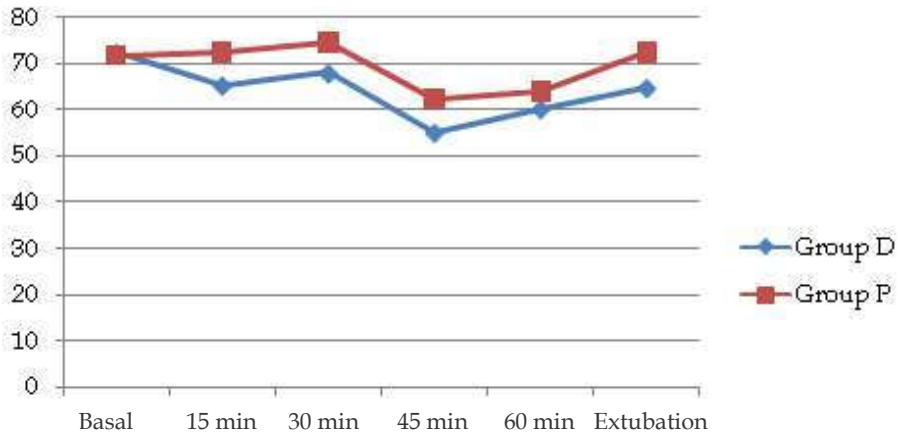
Results

No difference in the age, sex ratio and body weight was present between the groups. Shows (**Table 1**) Mean baseline heart rate was 72.35 ± 1.69 in group D and 71.8 ± 3.25 in group P ($p = 0.414$). Mean arterial pressure [MAP] at baseline was 91.97 ± 4.53 for Group D and 93 ± 2.46 for Group P ($p = 0.28$) both of which were statistically not significant. Heart rate and MAP gradually decreased following loading dose of injection dexmedetomidine I.V. in group D at *15 minutes* and throughout the duration of surgery at all the measured time intervals compared to Group P which was statistically significant ($p < 0.001$) displays (**Graphs 1 & 2**). The maximum fall in mean arterial pressure was seen *45 minutes* after the starting of the drug and was around 30% from baseline in group D (61.29 ± 3.76) compared to a fall of 28% in Group P (65.39 ± 3.18.) the fall being more in group D and significant stastistically. ($p < 0.05$). The lowest mean heart rate recorded in Group D was 55.05 ± 2.74 while in Group P it was 62.34 ± 2.94 the decrease being significant in Group D compared to group P ($p < 0.05$) at *45 minutes* after the start of the loading dose.

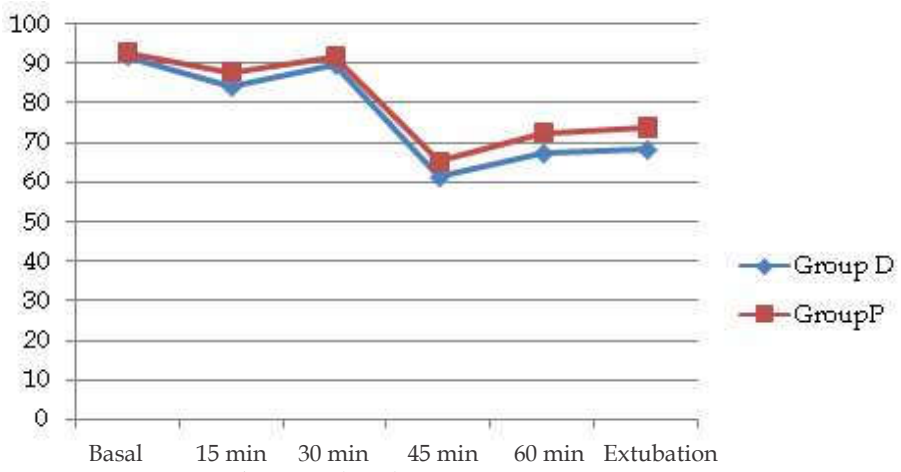
Table 1: Showing Age weight and sex of the patients

Parameter	Group D		Group II		*p* - value
Mean age	32.7		37.43		0.179
Weight in kilograms	Male	Female	Male	Female	0.184
	61.47	52.6	59.2	54.2	
Sex of patients	Male	Female	Male	Female	0.436
	15	15	12	18	

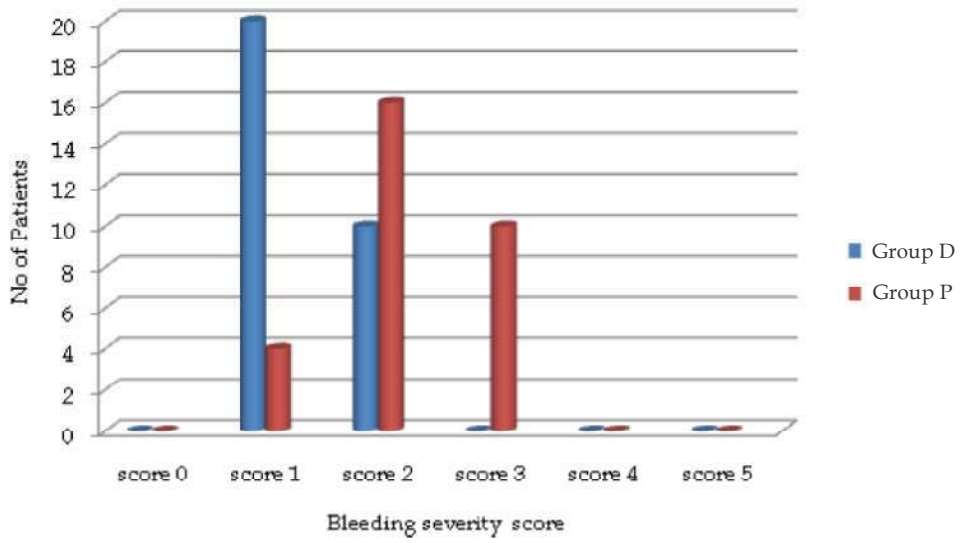
Bleeding severity score was 1 in 66.6% and 2 in 33.3% patients in Group D compared to 2 in 53.33% and 3 in 33.3% patients in Group P, more number of patients with lower scores in Group D, thus resulting in a shorter duration of surgery in Group D (*55.55 min ± 2.34*) when compared to Group P (*68.39 min ± 4.38*) which was statistically significant ($p < 0.01$) (**Graphs 3 & 4**). The volatile anesthetic agent needed in Group D was less Compared to Group P.



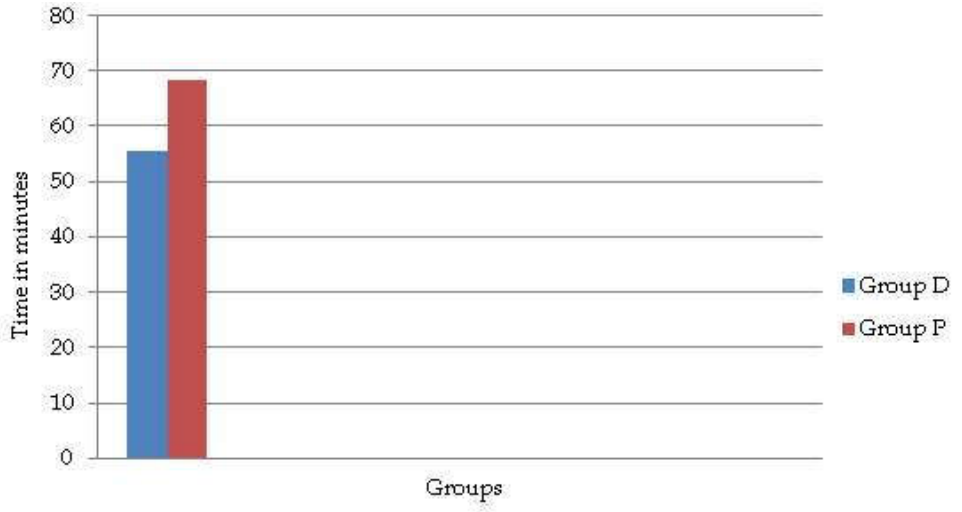
Graph 1: Heart Rate



Graph 2: Mean arterial pressure (MAP)



Graph 3: Bleeding severity score



Graph 4: Mean duration of surgery

Discussion

Bleeding associated with impairment of visibility in the intra-operative period and resultant prolongation of the surgical time is a problem seen in middle ear and nasal surgical procedures.[1,2,3,5] The reduction of MAP in the intra-operative period by around 30% of the basal values is called controlled hypotension.[1] This technique is employed in middle ear and nasal surgeries, operation of spine, head and neck surgical procedures,

In neurosurgery and orthopedic surgeries that are associated with major bleeding. Controlled hypotension in addition to improving the surgical visibility also reduces the need for blood transfusions by reducing the blood loss during surgery.[13,14] The drugs used to reduce the MAP should be specific, easy to titrate, have minimal or no interactions with other drugs with the duration of action being short.[15] The drugs used for producing controlled hypotension act by mainly by reducing the vascular tone.[5] Opioids like remifentanyl, volatile anesthetic agents, vasodilators like sodium nitroprusside and nitroglycerine are used with certain advantages and disadvantages.[8-10] α_2 agonist clonidine was used in many studies to reduce the bleeding during middle ear and nasal surgery.[15] A selective α_2 receptor agonist dexmeditomidine was approved for human use by the FDA in 1999. Clonidine the α_2 adrenergic receptor agonist has α_2:α_1 binding ratio of 220:1 [partial α2] with a elimination half life of eight hours while dexmeditomidine has α_2:α_1 of 1620:1 [full agonist of α_2] with elimination half life being 2–2.5 hours. Hence, dexmedetomidine is a preferred drug over clonidine.[11] Dexmedetomidine reduces the

blood pressure and bleeding by α_2 receptor mediated decrease in the norepinephrine release with resultant symphatholysis.[4] We selected the loading dose of *1 µg/kg* along with a maintenance dose of *0.5–0.8 µg/kg/hour* based on the results of the previous studies.[1,4,5]

The basal MAP was not different significantly amongst the groups. A reduction in the MAP was observed in the Group D, from a mean of 91.97 ± 4.53 to 61.29 ± 3.76 with maximum reduction seen at *45 minutes* after the starting of the dexmeditomidine and in the Group P also a fall of MAP was present from a basal mean of 93 ± 2.46 to 65.39 ± 3.18, with a maximum fall at *45 minutes* after the infusion. However, the fall in the Group D was significantly lower when compared with group P at all the time intervals. Ayoglu *et al.* in their study done to know the effectiveness of dexmedetomidine on blood loss in septoplasty and tympanoplasty found dexmedetomidine to cause a fall in blood pressure from the basal values.[1] In studies done to assess the effects of dexmedetomidine in patients subjected to laparoscopic surgeries Vora KS[16] *et al.* and Panchgar V *et al.*[17] noted a significant fall in the MAP in patients who received dexmedetomidine when compared to placebo. Durmus *et al.*[5] in the study of dexmedetomedine versus placebo in patients undergoing tympanoplasty reported a fall in blood pressure in both the groups without a significant difference which is in contrast to our findings. The higher fall in MAP in Group D can be attributed to dexmedetomidine mediated symphatolysis with a decrease in the vascular tone. Durmus *et al.*[5] used nitroglycerine infusion along with isoflurane to maintain lower levels of MAP in both the groups. Hence, there was a fall in MAP in both the groups. The bleeding severity score obtained by questioning the surgeons was lower in patients in the Group D. 66.6% (20 patients) had a score of 1 and 33.3% (10 patients) had a score of 2. In the placebo group the score was higher 13% (4 patients) had a score of 1, 53% (16 patients) had a score of 2, 33% (10 patients) had a score of 3. Significantly higher number of patients had a score of 1 in the group D. ($p < 0.05$). Ayoglu *et al.*, Durmus *et al.*[5] also reported a lower surgical bleeding scores in dexmedetomidine groups. Shams *et al.* in the study comparing dexmedetomidine and esmolol administration in FESS noticed a lower surgical bleeding scores when dexmedetomidine was used.[4] Lower scores for severity surgical bleeding can be due to a decrease in the MAP and bleeding in the intra-opertive period. We also noted a significant reduction in the surgical time in Group D which could be due to decreased bleeding and better visibility of the operating field. There was also a reduction in the mean heart rate in Group D which reduced to 55.05 ± 2.74 from 72.35 ± 1.69 at *45 minutes* after the start of dexmedetomidine. The mean heart rate in Group P was 71.8 ± 3.25 before the start of the infusion and reached the lowest of 62.34 ± 2.94 at *45 minutes* after the placebo administration. The fall was more in Group D which again is due to symphatholysis caused by dexmeditomidine. Ayoglu *et al.* [1], Durmus *et al.*[5], Vora KS *et al.*[16] and Panchgar V *et al.*[17] also observed a decrease in the heart rate when Dexmedetomidine was administerd. The requirement of isoflurane to decrease the intra-operative MAP and bleeding was higher in the Group P compared to Group D.

Conclusion

Dexmedetomidine used as an intravenous loading dose pre-operatively along with maintenance during tympanoplasty and FESS surgery reduces the MAP, intra-operative bleeding, surgical time, heart rate and requirement of volatile anesthetic.

Source of support: Nil

Conflicts of interest: Nil

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Peri-operative High Sensitive C-reactive Protein for Prediction of Cardiovascular Events after Coronary Artery Bypass Grafting Surgery in Left Ventricular Dysfunction Patients: A Prospective Observational Study

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Abstract

High sensitivity C-reactive protein is inflammatory marker having predictive value in both stable and unstable angina as well as in the acute phase after coronary artery bypass grafting. Many studies have evaluated the prognostic value of CRP for predicting post-operative outcome, most have focused on pre-operative CRP levels, which cannot reflect the inflammatory reactions induced by surgery itself. Here author hypothesized that post-operative CRP elevation, reflecting surgery-induced inflammatory reactions, is related to the occurrence of post-operative major adverse cardiovascular and cerebral events (MACCE) in patients undergoing off-pump coronary artery bypass surgery (OPCAB). *Objective:* To better understand the current state and application of high sensitivity C-reactive protein (hs-CRP) in clinical practice. To establish excellence of hs-CRP level as a prognostic marker in low EF heart patients. We have done prospective observational study in peri-operative period of 100 patients with stable ischemic heart disease and left ventricular dysfunction (EF < 35%) who underwent off pump CABG to ascertain whether an activation of the inflammatory system during surgery, detected by elevated serum hs-CRP, has any association with prognosis. *Result:* In patients with pre-operative hs-CRP ≥ 1.0 mg/dl, the cumulative event incidence was 38% compared to 15% in patients with levels pre-operatively of hs-CRP less than 1.0 mg/dl. Post-operative hs-CRP has no significant difference. *Conclusion:* Author conclude that increased pre-operative hs-CRP > 1.0 mg/dl predict in hospital cardiac and cerebrovascular morbidity and mortality. There is increase in post-operative hs-CRP but it is not statistically significant to conclude it as prognostic marker for predicting post-operative morbidity.

Keyword: C-reactive Protein; CABG; Prognosis; Inflammation.

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Introduction

Coronary Artery Bypass Graft (CABG) is the most common cardiac surgery which has both early and late post-operative complications.[1] Early complications include stroke, myocardial infarction, hemodynamic instability and long ICU stay.[2] Atherosclerosis, underlying cause of most Coronary Heart Disease, is basically Systemic as well local inflammation in arterial wall and

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shoulder region of plaque is heavily infiltrated with inflammatory cells.[3,4] As it is inflammation, inflammatory markers must be elevated across the clinical spectrum of atherosclerotic coronary artery disease.[5,6]

High sensitive C-reative Protein (hs-CRP) is used to detect the low level inflammation when CRP is within the normal range. Elevation of hs-CRP is associated with a poor prognosis in patients with acute myocardial infarction (AMI).[7] The recognition that active inflammatory processes may destabilize the fibrous cap tissue, thus triggering plaque rupture and enhancing the risk of coronary thrombosis.[8,9] Many studies have evaluated the prognostic value of CRP for predicting post-operative outcome, most have focused on pre-operative CRP levels, which cannot reflect the inflammatory reactions induced by surgery itself.[10,11]

In current study, author hypothesized that peri-operative hs-CRP elevation is related to the occurrence of post-operative major adverse cardiovascular and cerebral events (MACCE) in patients undergoing Off-pump Coronary Artery Bypass (OPCAB) surgery with left ventricular dysfunction. Author investigated the predictive value of a peri-operative high sensitivity CRP on 30 days mortality after elective OPCAB surgery.

They studied 100 patients with stable ischemic heart disease and left ventricular dysfunction (EF < 35%) who underwent off pump CABG to ascertain whether an activation of the inflammatory system during surgery, detected by elevated serum hs-CRP has any association with prognosis.

Materials and Methods

This study was done at tertiary care hospital. Study population of 100 patients were enrolled in following approval by the local ethical committee approval and getting informed, written consent of patients. This is prospective observational study.

Inclusion Ccriteria

Patients scheduled for off-pump Coronary Artery Bypass Grafting (CABG) surgery, less than *75 years* and with left ventricle ejection fraction less than 35%.

Exclusion Criteria

Chronic obstructive pulmonary disease, recent myocardial infarction, acute or chronic renal disease (serum creatinine > 2 *mg/dl*), chronic liver disease (total bilirubin > *3 mg/dl*), treatment with intravenous nitrates or inotropes before surgery, redo cardiac surgery, treatment with steroids in the previous six months, previous percutaneous coronary intervention, cerebrovascular accident during the year prior to the study, current inflammatory condition or history of a neoplastic condition.

The number, type and severity of diseased coronary arteries were determined based on angiography of the patient. Artery was considered to be diseased if the stenosis was equal or greater than 60% of the luminal diameter.

Anesthesia and Surgery

A single surgical and anesthesia team involved incurrent study. All patients underwent general anesthesia according to standardized protocol. After endotracheal intubation, 50% O_2, 50% air, and 1% to 2% sevofluranewas used for all patients. Antifibrinolytic agents were not used. Intra-operative TEE was done to document regional wall motion abnormality. Patients were transferred to the surgical Intensive Care Unit (ICU) after CABG and extubated there only after achieving extubation criteria. Patients older than *60 years* with a hemoglobin value less than *9 g/dl* and patients aged *60 years* or less with a hemoglobin value less than *8 g/dl* received packed red blood cells. Patients with a tendency to bleed were treated by transfusion of fresh frozen plasma and platelet concentrate. Inotropes were used only when hemodynamic stabilization could not be achieved by fluid administration or when there was other evidence of impaired contractility. In case of an insufficient response to inotropes, intra-aortic balloon counter pulsation was initiated at the discretion of intensivist.

Data collection

Fasting blood samples were collected from a peripheral vein before the operation. Post-operative blood samples were taken from indwelling CVP line. Peri-operative White Blood Cells (WBC), Platelets (PLT), Hemoglobin (Hb), S. creatinine, S. total bilirubin, SGOT and SGPT levels were measured by certified technician in the central biochemical and clinical laboratory. Pre-operative hs-CRP was taken within *3 days* prior to surgery and Post-operative Troponin I and hs-CRP level was measured at *12 and 24 hours* post-operative from central vein sample. A highly sensitive CRP (hs-CRP) analysis was performed using the commercially available kit of abbott CRP vivo an

automated blood test that uses particle-enhanced immunoturbidimetric method to quantify CRP in serum samples.

Definition of post-operative MACCE (Major adverse cardiovascular and cerebral events).

The primary endpoint was post-operative MACCE, which was defined as a composite of death from cardiac causes and stroke. Cardiac cause include MI, cardiac arrhythmia, or heart failure caused primarily by a cardiac problem. Stroke was defined as a new ischaemic or hemorrhagic cerebrovascular accident with a neurological deficit lasting more than *24h*. The diagnosis of MI was based on the associated with cardiac biomarker levels more than five times the upper reference limit.

Recent myocardial infarction (MI) was defined as myocardial infarction less than *30 days* at the time of surgery.[12] Patients were followed up to *30 days* after surgery and events recorded include:

(1) Death from cardiovascular causes.[13]

(2) Ischemic stroke[13] (defined as new ischemic or hemorrhagic cerebrovascular accident with a neurological deficit lasting more than *24h* with definite image evidence by head computer tomography).

(3) Hemodynamic instability due to Low Output Systemic heart failure[14] (LOF) (defined as needing one of the following: Intra-operative Intra-aortic Balloon Pump (IABP), return to graft revision, or ≥ two inotropes at *48 hours* post-operatively).

(4) Myocardial infarction or damage[15,16] (defined as elevated troponin I (Tn I) greater than *10.0 µg/l* at *12 hours* after surgery associated with characteristic Electrocardiographic (ECG) changes (development of new Q waves or new persistent ST-T change) or echocardiographically documented new dyskinetic-akinetic segment).

Use of inotropic agents and Intra-aortic Balloon Pump (IABP), Mechanical ventilation (MV) duration, lengths of Intensive Care Unit (ICU), hospital stay, number of grafts and peri-operative red blood cell transfusion were recorded. All data were collected prospectively.

Deaths were classified as either cardiac or non-cardiac. Deaths that could not be classified were considered cardiac. Hospital mortality is defined as all deaths within *30 days* of surgery, irrespective of where the death occurred, and all deaths in the hospital after *30 days* among patients who had not been discharged after undergoing surgery.

Results

Categorical variables are presented as numbers and percentages and analysed using the χ_2 test. Continuous variables are assessed for normal distribution and presented as means and standard deviation. Continuous variables are compared using student's *t*-test for normally distributed variables and the mann-whitney U test for non-normally distributed variables. The level of significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS, version 20.0 (Chicago, IL, USA).

In current study, both the groups were comparable with regards to age, sex, weight, height, body surface area, left ventricular ejection fraction, comorbidities, coronary artery involvement and medical management ($p > 0.05$), below shows (**Table 1**). During the first *30 days* after surgery, 78 patients were free from observed events and 22 patients developed following cardiovascular events: 8 (36.36%) had myocardial damage or infarction, 8 (36.36%) had low output heart failure, 4 (18.18 %) suffered cerebrovascular accident and 2(9.09%) patients were dead.

Table 1: Demographic and medication data according to Major Adverse Cardiovscular and Cerebral Events (MACCE).

Data	Without events (n = 78)	With events (n = 22)	*p* - value
Demographics			
Age, years	57.54 ± 8	54.64 ± 7.47	0.131
Gender,			
M	65	19	0.98
F	13	3	
BSA, m^2	1.67 ± 0.17	1.67 ± 0.15	0.954
Comorbidities			
DM	15	4	0.8439
HTN	6	1	0.9698
DM + HTN	6	1	0.9698
Angiography			
SVD	5	2	0.9698
DVD	30	9	0.9684
TVD	43	11	0.854
Echocardiography			
LVEF %	30.26 ± 5.22	29.78 ± 5.46	0.704
Medications			
Beta blockers	59	19	0.4349
ACE inhibitors	30	8	0.9445
Nitrates	19	6	1
Statins	55	13	0.4499
Diuretics	28	7	0.9194
Aspirin	50	12	0.5707

The impact of pre- and intra-operative clinical variables, according to chi-square test, on combined post-operative cardio-vascular event is shown in belo shows (**Table 2 & 3**). There is significant correlation of pre-operative hs-CRP with blood transfusion, ventilation duration, ICU stay and

Table 2: Clinical data according to Major Adverse Cardiovscular and Cerebral Events (MACCE).

Data	Without events (*n* = 78)	With events (*n* = 22)	*p* – value
Hematology			
WBC/*cmm*	9676.54 ± 2654.74	9308.19 ± 2351.67	0.558
Post-op WBC/*cmm*	14674.62 ± 4963.73	14683.64 ± 5296.97	0.994
Hemoglobin, *gm/dl*	12.66 ± 1.63	12.86 ± 2	0.636
Post-op Hemoglobin, *gm/dl*	10.9 ± 1.29	10.54 ± 1.41	0.258
Platelet/*cmm*	293826.93 ± 98296.93	269609.1 ± 64739.7	0.279
Post-op Platelet/*cmm*	159903.85 ± 85962.32	150318.19 ± 50930.82	0.62
Pre-creatinine, *mg/dl*	0.99 ± 0.29	1.02 ± 0.26	0.615
Creatinine, *mg/dl*	1.093 ± 0.307	1.164 ± 0.44	0.392
Pre-Billirubin, *mg/dl*	0.85 ± 0.44	0.77 ± 0.56	0.482
Post-op Billirubin, *mg/dl*	1.43 ± 0.97	1.25 ± 1.11	0.473
Pre-hs-CRP, *mg/dl*	0.7 ± 0.69	1.6 ± 2.35	0.03
Post-op hs-CRP *12 hr, mg/dl*	5.81 ± 4.32	4.58 ± 3.83	0.231
Post-op hs-CRP *24 hr, mg/dl*	12.07 ± 7.39	12.76 ± 6.68	0.693
Troponin I, µg/l	1.45 ± 2.15	7.47 ± 7.52	0.0001
RBS, *mg/dl*	175.22 ± 157.06	136.37 ± 29.82	0.253
RBS *12 hr, mg/dl*	165.15 ± 38.65	161.69 ± 36.75	0.709
RBS *24 hr, mg/dl*	163.42 ± 28.71	171.87 ± 44.35	0.287
Pre-Lactate, *mmol/l*	1.41 ± 0.52	1.44 ± 0.86	0.849
Post-op Lactate *12 hr*, *mmol/l*	3.03 ± 1.74	4.2 ± 2.64	0.15
Post-op Lactate *24 hr, mmol/l*	2.22 ± 0.78	2.63 ± 0.89	0.32
Pre-Ph	7.39 ± 0.04	7.39 ± 0.04	0.888
Post-op Ph *12 hr*	7.37 ± 0.05	7.39 ± 0.06	0.293
Post-op Ph *24 hr*	7.38 ± 0.04	7.36 ± 0.05	0.067
SVO2 %	70.15 ± 8.44	69.23 ± 7.27	0.643
Post-op SVO_2 *12 hr*, %	67.97 ± 7.44	69.21 ± 6.46	0.478
Post-op SVO_2 *24 hr*, %	67.62 ± 6.66	66.6 ± 7.18	0.538
Surgery			
Number of grafts	2.72 ± 0.83	2.5 ± 0.68	0.256
RBC transfusion, unit	1.26 ± 1.47	2.37 ± 1.82	0.004
Ventilation time, hours	5.99 ± 4.22	16.96 ± 18.85	< 0.0001
ICU Stay, days	3.33 ± 1.04	6.46 ± 7.38	< 0.0001
Hospital stay, days	6.81 ± 2.56	9.55 ± 6.62	0.004

Table 3: Demographic and medication variable according to pre-op hs-CRP > *1.0 mg/dl* or ≤ *1.0 mg/dl*.

Data	Pre-op hs-CRP < *1 mg/dl* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/dl* (*n = 29*)	*p* - value
Demographics			
Age, years	57.17 ± 7.1	56.25 ± 9.83	0.599
Gender,			
F	14	2	0.1983
M	57	27	
BSA, m^2	1.67 ± 0.16	1.67 ± 0.17	0.835
Comorbidities			
DM	15	4	0.5705
HTN	5	2	0.6713
DM + HTN	4	3	0.6848

Data	Pre-op hs-CRP < *1 mg/dl* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/dl* (*n = 29*)	*p* - value
Angiography			
SVD	4	3	0.6848
DVD	29	10	0.7144
TVD	38	16	0.9436
Echocardiography			
LVEF %	29.93 ± 5.11	30.69 ± 5.63	0.514
Medications			
Beta blockers	55	23	0.9491
ACE inhibitors	26	12	0.8275
Nitrates	19	6	0.7027
Statins	48	20	0.9172
Diuretics	28	7	0.2208
Aspirin	47	15	0.2602

Table 4: Clinical data according to Pre-op hs-CRP < *1.0 mg/dl OR* ≥ *1.0 mg/dl*

Data	Pre-op hs-CRP < *1 mg/l* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/l* (*n = 29*)	*p*- value
Hematology			
WBC/*cmm*	9626.62 ± 2442.87	9519.32 ± 2946.92	0.852
Post-op WBC/*cmm*	14914.09 ± 5039.57	14095.18 ± 4981.3	0.461
Hemoglobin, *mg/dl*	12.75 ± 1.75	12.58 ± 1.63	0.655
Post-op Hemoglobin, *mg/dl*	10.83 ± 1.37	10.78 ± 1.19	0.841
Platelet/*cmm*	296161.98 ± 98910.89	269737.94 ± 71430.33	0.195
Post-op Platelet/*cmm*	157759.16 ± 85470.43	157882.76 ± 63717.8	0.994
Pre-Creatinine, *mg/dl*	1 ± 0.3	0.98 ± 0.24	0.833
Creatinine, *mg/dl*	1.122 ± 0.36	1.074 ± 0.271	0.524
Pre-Billirubin, *mg/dl*	0.84 ± 0.49	0.8 ± 0.4	0.695
Post-op Billirubin, *mg/dl*	1.44 ± 1.03	1.27 ± 0.93	0.457
Post-op hs-CRP *12 hr, mg/dl*	5.34 ± 4.02	6.02 ± 4.76	0.47
Post-op hs-CRP *24 hr, mg/dl*	11.93 ± 7.27	12.95 ± 7.13	0.525
Troponin I, µg/l	2.45 ± 4.56	3.58 ± 4.93	0.275
RBS, *mg/dl*	174.17 ± 164.79	148.32 ± 32.37	0.405
RBS 12 hr, mg/dl	164.67 ± 38.49	163.69 ± 37.73	0.908
RBS *24 hr, mg/dl*	67.43 ± 6.78	67.29 ± 6.83	0.926
Pre-Lactate, *mmol/l*	1.4 ± 0.56	1.46 ± 0.72	0.635
Post-op Lactate *12 hr, mmol/l*	3.03 ± 1.7	3.93 ± 2.55	0.041
Post-op Lactate *24 hr, mmol/l*	2.34 ± 0.87	2.22 ± 0.89	0.536
Pre-Ph	7.39 ± 0.04	7.38 ± 0.04	0.093
Post-op Ph *12 hr*	7.37 ± 0.05	7.38 ± 0.05	0.369
Post-op Ph *24 hr*	7.38 ± 0.04	7.37 ± 0.05	0.302
Surgery			
Number of grafts	2.68 ± 0.76	2.66 ± 0.9	0.905
RBC transfusion, Units	1.31 ± 1.51	1.97 ± 1.77	0.063
Ventilation time, *hrs*	7.17 ± 9.09	11.42 ± 13.02	0.066
ICU Stay, days	3.69 ± 2.4	4.83 ± 5.87	0.167
Hospital Stay, days	7.41 ± 3.22	7.42 ± 5.45	0.995
MACCE	11	11	0.0284

hospital stay. Twenty nine patients had elevated serum concentration pre-operatively of hs-CRP ≥ *1.0 mg/dl* ($p = 0.028$). (**Table 4)** shows the distribution of other pre-operative variables according to high sensitivity CRP less than 1.0 mg/dl or ≥ 1.0 mg/dl. With preoperative hs-CRP ≥ 1.0 mg/dl, the cumulative event incidence was 38% compared to 15% in patients with levels pre-operatively of hs-CRP less than *1.0 mg/dl*. Serum concentration of pre-operative hs-CRP ≥ *1.0 mg/dl* was independent predictors of combined cardiovascular event after CABG surgery. Post-operative lactate at *12 hour* and ventilation time is significantly affected by pre-operative hs-CRP ≥ *1.0 mg/dl*.

Discussion

As far as author knows no study has been done for prediction of cardiovascular events in patients with dysfunctional heart undergoing CABG surgery based on pre and post-operative hs-CRP. In current study, author concluded that pre-operative serum concentrations of hs-CRP > *1.0 mg/dl* is associated with a significantly increased risk of overall post-operative cardiac death, myocardial infarction, low cardiac output syndrome and cerebrovascular accidents. Immediate post-operative hs-CRP does not appear to be a useful biomarker in the outcome after cardiac surgery as pre-operative hs-CRP.

CRP has been shown to be a strong predictor of early and long-term outcome after percutaneous coronary intervention and peripheral vascular surgery.[17,18] A pre-operative CRP > *0.3 mg/dl* is associated with a significantly increased risk of late all-cause mortality, cardiac death. As vulnerable plaque is probably responsible for approximately half of peri-operative MI.[19,20]

There are very few authors who used hs-CRP which is used in our study. Serum concentration of hs-CRP ≥ *3.3 mg/l* was an independent risk factor of post-operative combined cardiovascular event in patients undergoing CABG surgery.[21] But average ejection fraction was 50% in this study. Cardiovascular events happen more often in dysfunctional heart. So, author studied predictive value of hs-CRP in dysfunctional heart patient undergoing CABG in Indian continent. And author find out that cut off limit of hs-CRP as independent risk factor for cardiovascular event is on lower side in low EF patients.This might be used to refine the predictive value of scores such as the Euroscore.[12] Further studies with larger number of patients are needed to allow generalization of our findings.

There is study showing no correlation of post of hs-CRP and post-operative outcome,[22] in valvular and coronary surgery. But here author have studied only in coronary surgery as this patients are more vulnerable for atherosclerosis plaque. In current study, post-operative hs-CRP at *24 hr* is higher in patient having cardiovascular event but statistically not significant. So if we follow it Post-erative day 2 & 3, we might get statistically significant result. But that is limitation of our study.

Factors that can affect peri-operative hs-CRP like pre-operative statin and other drug treatment, peri-operative total count, left ventricular ejection fraction and other demographic and clinical data are similar in both group of patients. There is always a limitation when relatively rare complications are analysed. Hs-CRP may be adversely affected by local or systemic infection which limits its utility for prognostic marker.[23] It is recommended that patients with a CRP of > *1 mg/d1* in the presence of active infection, should have the test repeated in *2 weeks*, as the clinical significance of the test is questionable.[23] Infections would be expected to increase false negative test results and decrease the utility of the test. In our study, pre and post-operative total WBC count and platelet count is comparable so there is less chance of infection associated inflammatory response. Though pre-operative hs-CRP is related with MACCE, it has no correlation with post-operative renal dysfunction or acute kidney injury.

A number of studies implicate CRP as an important mediator in the generation of atheromatous coronary plaque, including uptake of low-density lipoprotein by macrophages, triggering increased expression of endothelial cell surface adhesion molecules, and activating complement system proteins.[24,25] Moreover, although there is strong evidence that putative CRP gene single nucleotide polymorphisms influence systemic CRP levels, an independent association between these CRP single nucleotide polymorphisms and adverse cardiovascular events has not been definitively established[26]. Confirmation of a direct causal relationship between post-operative hs-CRP and cardiovascular outcomes will require further investigation.

Another intra-operative factor that is significantly associated with MACCE is peri-operative RBC transfusion. Transfusion of red blood cells remained an independent risk factor of combined cardiovascular event after CABG surgery.[27] Transfusion of stored RBC can augment inflammation by various mechanisms and that might have been reflected in post-operative CRP levels in our study. Another possible explanation is that significant bleeding requiring RBC transfusion might have caused hypoperfusion which can lead to MACCE. Additionally, intra-operative hypoperfusion triggers inflammatory reactions and consequently increases post-operative serum CRP levels.

Low ejection fraction patients may be limitation and one may argue that the current findings may be not generalized to the contemporary surgical population. Anyway, the pre-operative high sensitivity CRP ≥ *to 1.0 mg/dl* is associated with poor outcome after elective OPCABG surgery in dysfunctional heart.

Conclusion

In this study, author conclude that increased pre-operative hs-CRP > *1.0 mg/dl* predict in hospital cardiac and cerebrovascular mortality and morbidity in low EF patients undergoing CABG. Post-operative increase in hs-CRP may be due to inflammatory response of surgery. But its prognostic value for predicting post-operative morbidity needs further randomised control study. These findings may allow for more objective risk stratification of patients who present for elective surgical coronary revascularization.

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Original Research Article

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A Comparative Study of 0.0625% Levobupivacaine with Fentanyl Versus 0.1% Ropivacaine with Fentanyl for Continuous Epidural Labor Analgesia

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Abstract

Background: Ropivacaine and Levobupivacaine are newer local anesthetic agents in obstetric practice for labor epidural analgesia which have got advantages of less motor blockade and systemic toxicity compared to Bupivacaine. *Objective:* To compare the efficacy of equipotent doses of Ropivacaine 0.1% and Levobupivacaine 0.0625% with fentanyl as continuous infusion for labor epidural analgesia. *Study Design:* A Prospective randomized control trial. *Methods:* After obtaining the institutional ethics committee approval, Patients who met the inclusion criteria were randomly allocated to group B and group R (20 patients in each group) by computer generated random numbers. Patients were randomly assigned to receive either 10 ml of 0.2% ropivacaine or 10 ml of 0.125% levobupivacaine followed by infusion of 0.1% ropivacaine with fentanyl 2 mcg/ml or 0.0625% levobupivacaine with fentanyl 2 mcg/ml at 8 ml/hr continuous epidural infusion. Visual analogue scale (VAS) before epidural bolus dose and throughout the labor were recorded. Maternal heart rate, blood pressure, oxygen saturation, fetal heart rate, maximum sensory level achieved and degree of motor blockade were recorded every fifteen minutes. *Results:* The demographic variables were comparable between the two groups. There was no significant difference in the onset of pain relief, VAS scores during the infusion and level of Sensory block. There was no difference found in the hemodynamic parameters, delivery outcome, patient satisfaction and neonatal outcome. *Conclusion:* Epidural Levobupivacaine provides good and effective analgesia as Ropivacaine for labor pain and hence, a good alternate local anesthetic in labor epidural analgesia with cost limitations.

Keywords: Epidural; Labor analgesia; Levobupivacaine; Ropivacaine.

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Introduction

Labor pain is one of the most severe pain which may lead to unpleasant experiences when not adequately treated and it may lead to devastating consequences in the presence of cardiac comorbidities in a patient. Labor analgesia is an age-old practice started in 1847 with ether by JY Simpson and historic incident in labor analgesia by chloroform administration to Queen Victoria by John Snow in 1853.[1] Even though

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various non-pharmacological and pharmacological methods are available for labor analgesia, epidural analgesia remain the gold standard and most practiced technique. The advantages are continuous and effective analgesia with minimal systemic side effects to mother and foetus compared to inhalational agents and systemic opioids. Also, it has got the advantage of conversion to anesthesia for cesarean section.

Lower concentrations of local anesthetics reduce the motor blockade and when combined with opioids like fentanyl improves the quality of analgesia.[2,3,4] Bupivacaine is the commonly used local anesthetic which provides good analgesia but with high motor blockade potential and cardiotoxicity on systemic absorption. Ropivacaine produces more sensory and less motor blockade than bupivacaine with less systemic toxicity.[5,6,7] Levobupivacaine is one of the newest local anesthetic with good sensory and minimal motor blockade effects and minimal cardiotoxicity.[8] This study is done to compare the efficacy of Ropivacaine and Levobupivacaine in providing epidural analgesia for labor.

Materials and Methods

This study was a prospective randomized double blinded control trial involving 40 parturients (20 in each group) in a tertiary care hospital after obtaining institutional ethics committee approval.

Primigravida as well as multigravida patients with previous normal delivery of age group between *18 and 35* belonging to ASA physical status I and II who were in active labor with cervical dilatation of *3 to 4 cm* were included in the study. Those who have contraindications to epidural block, failed epidural block and complications associated with pregnancy like preterm labor, multiple gestation and previous cesarean sections were excluded.

All the patients meeting the inclusion criteria were counselled for labor analgesia and informed consent obtained after explaining the procedure. History of the patient was collected and routine basic blood investigations done as per our hospital protocol. Patients were then randomly allocated into two groups (R and B) by computerized randomized list.

Before epidural placement 18G intravenous cannula was established in all patients and monitors like pulse oximeter and non-invasive BP were applied. Under strict aseptic precautions, lumbar epidural space identified by loss of resistance technique to air with 18G Tuohy needle and *10 ml* LOR syringe. Epidural catheter threaded 5 cm into the space and secured in position. Epidural test dose given after negative aspiration for blood or CSF. Initial bolus of *10 ml* of 0.2% Ropivacaine (group R) or 0.125% Levobupivacaine (group B) was given. Additional *5 ml* boluses were given if VAS score was more than 3 even after *15 mins* of initial bolus dose. Analgesia was maintained with continuous infusion of 0.1% Ropivacaine with *2 mcg/ml* fentanyl (group R) or 0.0625% Levobupivacaine with *2 mcg/ml* fentanyl (group B) at *8 ml/hr* using a syringe pump. Further boluses of *5 ml* of Ropivacaine 0.2% or Levobupivacaine 0.125% were given for breakthrough pain. The total number of boluses required were recorded. The study was concluded at the time of normal or assisted vaginal delivery or when decided for cesarean section. Epidural anesthesia was provided through the catheter in cases converted to cesarean section.

Both the patient and anesthesiologist in labor room were blinded to the study solutions. Various maternal parameters like pulse rate, systolic and diastolic blood pressure, oxygen saturation, level of sensory blockade, VAS score displays in (**Fig. 1**) and modified Bromage scale for motor blockade shows in (**Table 1**), Foetal heart rate was monitored continuously.

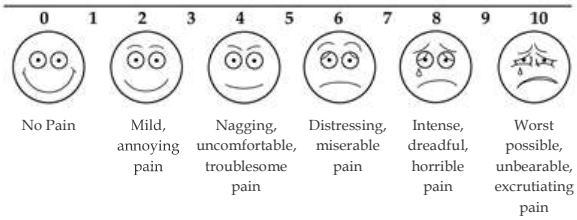

Fig. 1: Visual analog scale

Table 1: Assessment of motor block by modified Bromage scale

Grade 0	No motor block
Grade 1	Inability to raise extended leg, able to move knees and feet
Grade 2	Inability to raise extended leg and move knee, able to move feet
Grade 3	Complete motor block of the lower limbs

The clinical outcomes like time to achieve adequate pain relief (VAS ≤ 3), maximum sensory level attained, degree of motor block, duration of labor, mode of delivery, patient satisfaction, neonatal outcome (APGAR score) were studied and compared in both the groups.

Results

20 patients were studied in each group who were comparable in terms of demographic data like age,

weight, height and ASA physical status. Parity and cervical dilation at the onset of labor were also comparable between the groups.

The mean onset of pain relief in group B (*11.65 ± 1.60 mins*) though slightly less than in group R (*12.5 ± 1.39 mins*) displays in (**Fig. 2** and **Table 2**). This variable does not have any statistical significance difference ($p = 0.08$). Statistical analysis was calculated using student independent *t*-test. In group B 45% had a sensory level of T6 and 60% had T8 level, whereas in group R 50% had T8 and 45% had T6. The statistical analysis was done by Chi–square test and it was found to be statistically insignificant displays in (**Fig. 3**). On comparing the VAS score, there was a noticeable decrease in the pain levels after administration of epidural local anesthetic. The pain levels did not go above visual analog score of 3 during infusion in both the groups displays in (**Fig. 4**). The variation in pain scores did not have any statistical significance. The motor blockade was not present in both the groups and all patients had grade 0 in modified bromage scale and hence statistically insignificant.

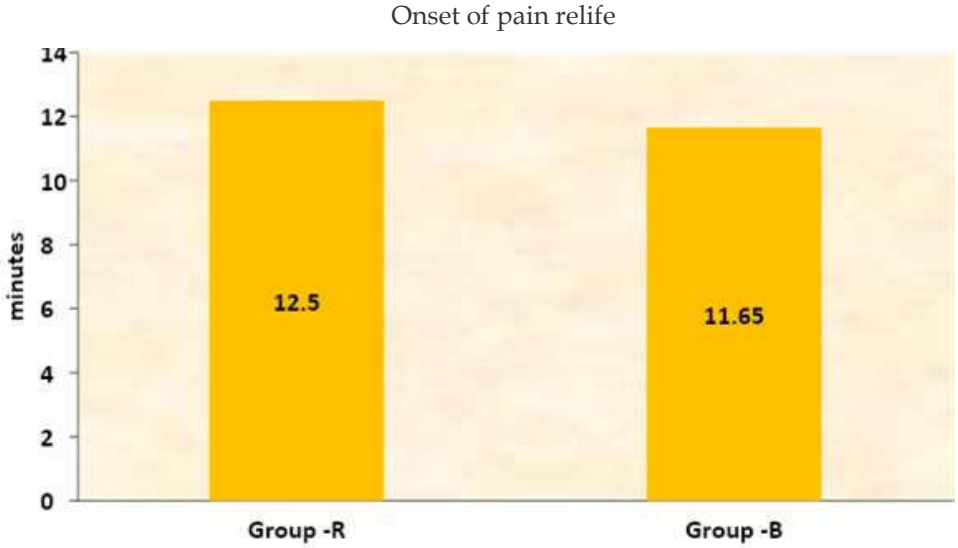

Fig. 2: Comparison of onset of pain relief between the two groups. Both groups were comparable with no statistical significance.

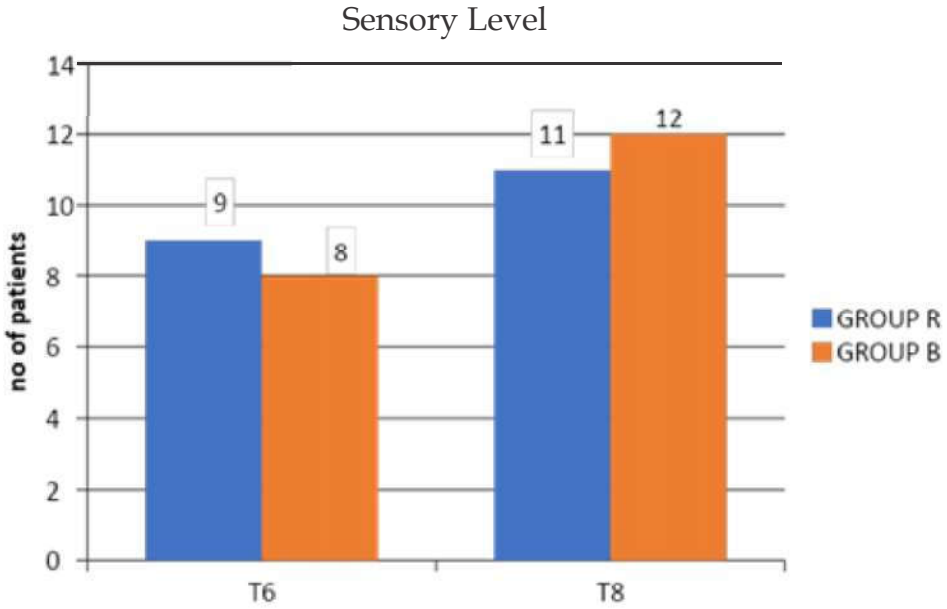

Fig. 3: Comparison of sensory level between the two groups. Both groups were comparable with no statistical significance.

Table 2: Comparison of various parameters between the groups

Parameters	Group B	Group R	*p* - value
Onset of analgesia (*min*)	11.65 ± 1.6	12.5 ± 1.39	*p* = 0.08*
Duration of labor (*min*)			
I stage	182.65 ± 21.99	183.50 ± 25.06	*p* = 0.91*
II stage	29.71 ± 2.22	30.39 ± 2.30	*p* = 0.38*
Nature of delivery (normal/assisted/ LSCS)	15/2/3	15/3/2	*p* = 0.81*
Patient satisfacation (Good/Fair/Poor)	14/6/0	14/6/0	*p* = 1.00*
APGAR Score (out of 10)			
1 *min*	7.85	7.80	*p* = 0.68*
5 *min*	8.90	8.85	*p* = 0.64*

*All are statistically insignificant

The mean duration of labor in 1st stage in group B (182.65 ± 21.99) though slightly less than in group R (183.50 ± 25.06) which carries no statistically significant difference ($p = 0.11$). The mean duration of 2nd stage of labor in group B (29.71 ± 2.22) though slightly less than in group R (30.39 ± 2.30) without any statistically significant difference ($p = 0.89$). Statistical analysis was calculated using student independent *t*-test.

The hemodynamic variables like pulse rate, systolic and diastolic blood pressure of the mother and fatal heart rate recorded at regular intervals were analysed between the groups at various time points and found to be comparable.

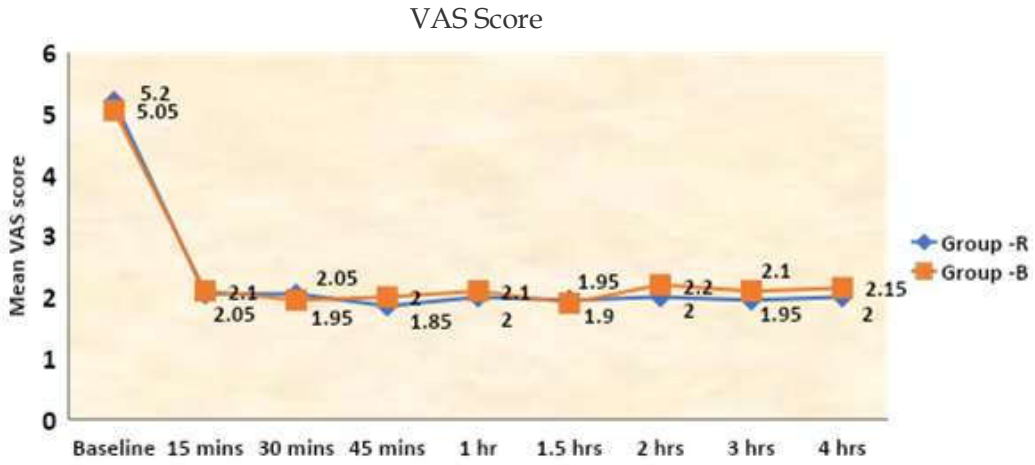

Fig. 4: Comparison of VAS score between the groups. Patients in both the groups had drastic reduction in VAS score after bolus dose and score of less than 3 was maintained throughout the labor and statistically insignificant when compared.

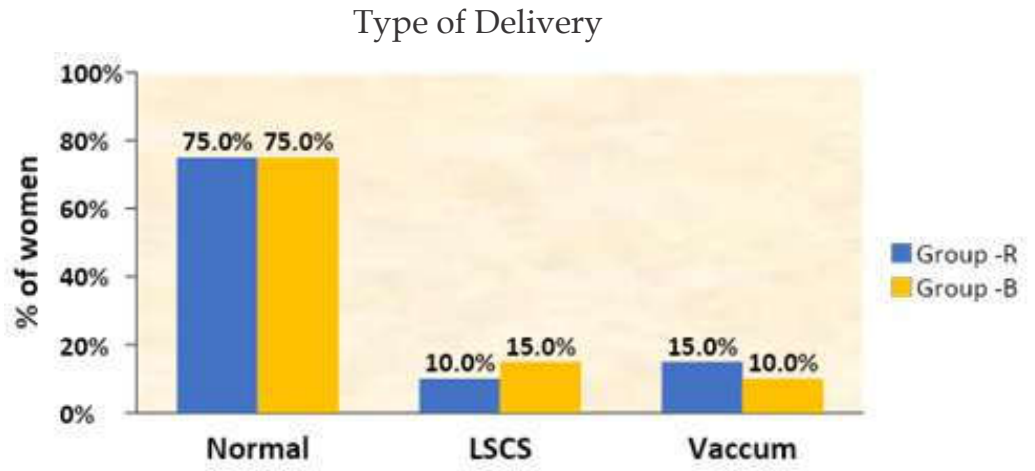

Fig. 5: Comparison of type of delivery between the two groups. Both groups were comparable with no statistical significance.

Fig. 6: Comparison of patient satisfacation between the two groups. Both groups were comparable with no statistical significance.

Group R had 75% of normal delivery, 10% had LSCS and 15% had vacuum where as in Group B, 75% of normal delivery, 15% had LSCS and 10% had vacuum displays in (**Fig. 5**). Their distribution among groups was not significant (p = 0.81) in statistical analysis calculated using chi-square test. The overall patient satisfaction was graded as good, fair and unsatisfactory. Group R as well as Group B, both groups had 70% good satisfaction and 30% fair satisfaction displays in (**Fig. 6**). Their distribution among groups was not statistically significant (p = 1.00) with chi-square test. The neonatal outcome was rated with APGAR score at *1 and 5 mins*. The chi-square test reveals that the values were not statistically significant at *1 and 5 mins*. Two patients in group R and one patient in group B had nausea. Hypotension was present in 2 patients in group R and 3 patients in group B. We observed that the complications in both the group were statistically insignificant in ANOVA two-way test.

Discussion

In our study, we used initial bolus of *10 ml 0*.125% Levobupivacaine and 0.2% ropivacaine and maintained with low concentration of equipotent doses of 0.0625% Levobupivacaine with fentanyl *2 mcg/ml* and 0.1% ropivacaine with fentanyl *2 µg/ml* at a rate of *8 ml/hr* as continuous infusion the parturients were comparable in regards to age, comorbid conditions, ASA grading, parity and Cervical dilatation in both the groups.

Pain Relief

In our study. we found that the mean VAS score was around 5.2 in Levobupivacaine group and 5.01 in ropivacaine group. This has been reduced to 2.01 in Levobupivacaine group and 2.05 in ropivacaine group *15 mins* after epidural administration of local anesthetic. The VAS score was further reduced to a minimum. There was no clinically demonstrable difference in the onset of pain relief. The patient satisfaction was also comparable between the two groups.

This was consistent with the results obtained by Supandji M[9] *et al*. when they compared 0.2% ropivacaine and 0.2% levobupivacaine. The Preblock visual analog scale (VAS) score and VAS score after five, ten, *15, 20, 25* and *30 min* from time (0) and VAS at time of request for additional analgesia (time) were recorded and it was found to be comparable in both the groups.

Purdie and McCrady in 2004[10] demonstrated that 0.1% ropivacaine and 0.1% levobupivacaine with 0.00002% fentanyl provided comparable pain relief labor epidural analgesia and also insignificant differences in terms of local anesthetic consumption, onset and duration of analgesia, sensory and motor blockade, mode of delivery, neonatal outcome and patient satisfaction. Similar results are encountered in other studies[11,12] comparing ropivacaine and levobupivacaine for labor analgesia.

Motor Blockade

Both Ropivacaine and Levobupivacaine did not cause motor blockade in our study as the concentrations used were low which was demonstrated in similar other studies.[9,10,11] Finegold *et al*.[13] and Halpern *et al*.[14] demonstrated the superiority of ropivacaine to bupivacaine regarding motor blockade in labor epidural analgesia but

Beilin *et al*.[15] found levobupivacaine produced less motor blockade than ropivacaine and bupivacaine. However, Wang *et al*.[16] observed no differences in motor blockade among bupivacaine, ropivacaine and levobupivacaine in low concentrations.

Mode of Delivery

In our study. we had comparable numbers in mode of delivery between Levobupivacaine group and Ropivacaine group with no statistical significance. Our study results coincide with the study done by Hui-Ling Lee *et al*.[12] comparing Levobupivacaine 0.06% and Ropivacaine 0.08% with fentanyl and found that there was no difference in mode of delivery in both the groups. Finegold *et al*.[13] observed an instrumental vaginal delivery rate of 18% in ropivacaine group and 28% in bupivacaine.

Fetal and neonatal outcome

In our study. the foetal heart rate during the process of labor analgesia was within normal limits. There was no incidence of post epidural foetal bradycardia. The APGAR score was also not statistically significant. This was consistent with the studies done by Hui Ling Lee *et al*.[12] and Beilein *et al*.[15] comparing ropivacaine and levobupivacaine.

Complications

The complications like nausea, vomiting and hypotension were observed in both the groups and it was found to be statistically insignificant.

Conclusion

Our study concludes that pain relief offered by epidural Levobupivacaine is as good and effective as epidural Ropivacaine. It is comparable in terms of pain relief, motor blockade, sensory level achieved, patient satisfaction and neonatal outcome. Hence, Levobupivacaine is an effective alternative to Ropivacaine in labor epidural analgesia with cost limitations.

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Presentation at a meeting: Nil

Conflicting Interest: Nil

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Original Research Article

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Efficacy of Intravenous Paracetamol for Attenuating Hemodynamic Response to Laryngoscopy and Intubation: A Prospective Randomized Study

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Abstract

Background and Aims: Laryngoscopy and endotracheal intubation violate the patients' airway reflexes and cause intense sympathetic activity. Literature suggests that this deleterious response may be blunted by drugs. Opioids are most commonly used for this purpose. However, there is no consensus regarding the best drug and best route of administration. Therefore, there has been a growing trend to find an effective substitute to lower these side effects as much as possible. Paracetamol is a non-opioid analgesic with COX-2 selective inhibiting property. The main purpose of our study was to evaluate the effect of pre-operative intravenous paracetamol on hemodynamic response to laryngoscopy and endotracheal intubation. *Methods:* After Institutional Ethical Committee clearance, 160 patients of American Society of Anesthesiologists (ASA) Physical Status I and II were enrolled in the study and divided into two groups. Group A received 1 gm paracetamol infusion (Labelled A1) in 100 ml volume whereas Group B received 0.9% normal saline infusion (B1) in 100 ml volume Intravenously (I.V.) thirty minutes prior to induction over fifteen minutes. Standard general anesthesia techniques were used for both groups. The hemodynamics were recorded at baseline, before induction, after induction, before laryngoscopy, immediately after intubation and thereafter 1, 3, 5, 7 and 10 inutes following intubation. After 10 minutes of intubation, Group A received the infusion labeled A2 (0.9% Normal saline in 100 ml volume) whereas Group B received the infusion labeled B2 (paracetamol 1 gm in 100 ml volume) over 15 minutes. *Results:* Both groups were similar in terms of age, sex, height, weight, Mallampati scores and American Society of Anesthesiologists (ASA) physical status. After 1 minute of laryngoscopy and intubation, significant increase in the heart rate was seen in both the groups. ($p \leq 0.05$) in Group A, the increase in mean heart rate produced by laryngoscopy and intubation was not statistically significant at 3 mins ($p \geq 0.05$) and remained insignificant at 5, 7 and 10 minutes after intubation. However, in Group B the increase in mean heart rate produced by laryngoscopy and intubation was significantly high at 3 min ($p \leq 0.0001$) and remained significant at 5, 7 and 10 minutes after intubation. There was significant fall in SBP, DBP and MAP ($p \leq 0.05$) from baseline after induction, laryngoscopy and after 1 minute of intubation in both Group A and Group B but inter group comparisons at these time points were statistically insignificant ($p \geq 0.05$). *Conclusion:* Administration of paracetamol (1 gram), thirty minutes prior to induction of anesthesia could not totally blunt all the cardiovascular responses to laryngoscopy and intubation, but it did show better control of heart rate after intubation.

Keywords: Anesthesia; Laryngoscopy; Intubation; Paracetamol.

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Introduction

Laryngoscopy and endotracheal intubation violate the patients' airway reflexes and cause intense sympathetic activity which lead to tachycardia, hypertension and dysrhythmias.[1] These effects have been reported since 1950, during intubation under lighter plane of anesthesia, which may be further complicated by hypoxia, hypercapnia or cough.[2,3] This response may also have deleterious effect on patients with raised intracranial and intraocular tensions.

Hemodynamic stability is an integral and essential goal of any anesthetic management plan. Increase in blood pressure and heart rate occurs most commonly from reflex sympathetic activity in response to laryngotracheal stimulation, which in turn leads to increase plasma norepinephrine concentration.[4] Literature suggests that this deleterious response may be blunted by drugs with different mechanisms of action like lignocaine, glossopharyngeal and superior laryngeal nerve blocks, calcium channel blockers, beta blockers, combined alpha-beta blockers, alpha blockers, peripheral vasodilators, narcotics, oral gabapentine and magnesium sulphate.[5]

However, there is no consensus regarding the best drug and best route of administration. Although opioids are most commonly used drugs for prevention of hemodynamic responses to intubation, these drugs are not cost effective and have unfavorable effects like nausea, vomiting, sedation and respiratory depression.[6] Therefore, there has been a growing trend to find an effective substitute to lower these side effects as much as possible.[7,8]

Paracetamol is a non-opioid analgesic and is in clinical use for last hundred years.[9] Paracetamol is, on average, a weaker analgesic than NSAIDs or COX-2 selective inhibitors but is often preferred because of its better tolerance.[10] Intravenous paracetamol has an onset and peak effect of *15 minutes* or less and a duration of analgesic effect between *4* and *6 hours*.[11,12] Recently the prodrug of paracetamol has been shown to have blunting effect on hemodynamic response to laryngoscopy and intubation.[13]

However, there is limited data about the effects of I.V. paracetamol on hemodynamics.Therefore, the main purpose of our study was to evaluate the effect of pre-operative intravenous paracetamol on hemodynamic response to laryngoscopy and endotracheal intubation.

Materials and Methods

This study was conducted in our hospital after approval from institutional ethics committee and informed consent. We included 160 patients between *18 and 60 years* of age belonging to American Society of Anesthesiologists class I and II having Mallampati grade of either I or II who underwent elective non-cardiac surgeries requiring general anesthesia with endotracheal intubation. Patients with known hypertension, autonomic neuropathy, diabetes mellitus or other endocrinopthy, patients taking cardioactive drugs, antiepileptic drugs or antipsychotic drugs and patients with anticipated difficult mask ventilation or laryngoscopy and all emergency surgical cases were excluded from the study.

All patients were provided with patient information sheet and written informed consent was obtained. Pre-anesthetic check up and investigations were done. The patients were kept fasting overnight after *10:00 pm* and received tablet ranitidine *150 mg* orally and tablet alprazolam *0.25 mg* orally as premedication the night before surgery. All patients were monitored using standard American Society of Anesthesiologists (ASA) monitors like non-invasive blood pressure (NIBP), pulse oximetry, and electrocardiography (ECG). Intravenous access was secured using an 18 G cannula in the forearm of the non-dominant hand.

Patients were randomized into two groups, either Group A or Group B, consisting of 80 patients each using computer generated random number table. Double blind technique was used in which both the anesthesiologist administering the drug as well as the patients were unaware as to which group the patient belonged to. One anesthesiologist labeled the intravenous (I.V.) infusions which were then administered to the patients by another anesthesiologist who did not know the contents of the infusion. The parameters were recorded by the second anesthesiologist.

Group A received *1 gm* paracetamol infusion (Labeled A1) in *100 ml* volume whereas Group B received 0.9% normal saline infusion (B1) in *100 ml* volume intravenously (I.V.) thirty minutes prior to induction over fifteen minutes. After pre-oxygenation with 100% O_2 for three minutes and premedication with injection Fentanyl *1 mcg/kg* intravenously (I.V.), the patients were induced with injection Propofol *2 mg/kg* I.V. and intubated with appropriate sized cuffed endotracheal tube with injection Vecuronium *0.1 mg/kg* I.V. after establishment of neuromuscular blockade confirmed with disappearance of single

twitch response with a nerve stimulator. The hemodynamics were recorded at baseline, before induction, after induction, before laryngoscopy, immediately after intubation and thereafter, *1, 3, 5, 7 and 10 minutes* following intubation. After *10 minutes* of intubation, Group A received the infusion labeled A2 (0.9% Normal saline in *100 ml* volume) whereas Group B received the infusion labeled B2 (paracetamol *1 gm* in 100 ml volume) over *15 minutes*.

Anesthesia was maintained with isoflurane (0.6 to 1%) in a mixture of O_2 and N^2O (1:2) and injection vecuronium bromide. Total intubation time (in seconds) was defined as the time from insertion of the tip of the endotracheal tube into the trachea, up to the time of tube confirmation.

Statistical Analysis

All statistical analysis was performed using Statistical Packages for Social Science version 19 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean (standard deviation) for quantitative variables like age, weight, SBP, DBP, HR. Independent sample *t*-test and Mann-Whitney tests were applied to compare the mean/median difference between groups for age, weight. The paired *t*-test was used to compare within-subject effect for HR and BP. $p < 0.05$ was considered as significant.

Results

A total of 160 patients were included in the study with 80 patients each in Group A (Paracetamol group) and Group B (Normal saline). However, four patients from Group A and five patients from Group B were excluded from the study as they needed more than one attempt for intubation. There was no statistical difference between the two groups in terms of age, sex, height, weight, Mallampati scores and American Society of Anesthesiologists (ASA) physical status shows in (**Table 1**).

Table 1: Baseline characteristics between the groups (mean ± SD)

Characteristics	Group A (n = 76)	Group B (n = 75)	p - value
Age (In years)	35.98 ± 0.22	35.50 ± 10.39	0.95
Sex (M/F)	33/43	31/44	0.87
Weight (Kg)	55.06 ± 8.61	54.4 ± 9.28	0.32
Height (In cms)	157.76 ± 9.62	158.4 ± 1.56	0.35
MPS (I/II)	19/57	17/58	0.85
ASA (1/2)	54/22	50/25	0.56

SD = Standard deviation; n = number of patients; ASA = American Society of Anesthesiologists; MPS = Mallampati score.

The baseline heart rates (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressures (MAP) were comparable in both the groups. The decrease in the mean heart rates after induction was also statistically insignificant in both the groups. ($p \geq 0.001$) after *1 minute* of laryngoscopy and intubation, significant increase in the heart rate was seen in both the groups. ($p \leq 0.05$) In Group A, the increase in mean heart rate produced by laryngoscopy and intubation was not statistically significant at *3 mins* ($p \geq 0.05$) and remained insignificant at 5, 7 and *10 minutes* after intubation.

However, in Group B the increase in mean heart rate produced by laryngoscopy and intubation was significantly high at *3 min* ($p \leq 0.0001$) and remained significantat *5, 7 and 10 minutes* after intubation. Shows (**Table 2**) the mean baseline values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were similar and statistically insignificant ($p > 0.05$) between Group A and Group B. There

Table 2: Mean Heart Rate at different pre-defined points of time

Heart Rate (beats per minute)			Intra Group (compared to the baseline)		Inter Group (compared between similar points of time)
	Group A Mean ± SD	Group B Mean ± SD	Group A p - Value	Group B p - Value	p - Value
Baseline	78.44 ± 13.39	80.24 ± 11.97			0.19
Before induction	78.34 ± 13.59	80.36 ± 11.60	0.48	0.47	0.16
After induction	77.32 ± 11.61	79.90 ± 12.28	0.29	0.43	0.20
Before laryngoscopy	78.22 ± 11.78	79.22 ± 12.46	0.45	0.30	0.31
1 min after intubation	84.28 ± 11.50	98.44 ± 12.74	0.04	< 0.0001	< 0.0001
3 min after intubation	84.05 ± 11.15	94.16 ± 13.56	0.07	< 0.0001	< 0.0001
5 min after intubation	81.60 ± 10.30	87.33 ± 12.22	0.06	0.0002	0.0013
7 min after intubation	80.46 ± 8.25	86.91 ± 11.64	0.052	0.0003	0.0003
10 min after intubation	78.57 ± 10.85	82.88 ± 11.75	0.69	0.007	0.012

SD = Standard deviation.

was significant fall in SBP, DBP and MAP ($p \leq 0.05$) from baseline after induction, laryngoscopy and after *1 minute* of intubation in both Group A and Group B but inter group comparisons at these time points were statistically insignificant ($p \geq 0.05$). The mean SBP, DBP and MAP at *3, 5, 7* and *10 minutes* showed no difference between Group A and Group B ($p \geq 0.05$) shows in (**Tables 3,4,5**), along with displays (**Graphs 1–3**).

Table 3: Mean SBP at different pre-defined points of time

SBP			**Within Group**		**Inter Group**
	Group A	**Group B**	**Group A**	**Group B**	
	Mean ± SD	**Mean ± SD**	***p* - V alue**	***p* - Value**	***p* - Value**
Baseline	122.57 ± 11.82	124.49 ± 11.96			0.11
Before induction	122.76 ± 11.99	123.88 ± 10.91	1.0	1.0	0.59
After induction	115.97± 11.03	116.25 ± 11.66	0.012	0.001	0.25
Before laryngoscopy	113.73 ±10.38	116.56 ± 11.63	0.001	0.002	0.85
1 min after intubation	131.54 ± 13.23	134.96 ±15.22	0.001	< 0.0001	0.32
3 min after intubation	126.16 ± 11.86	126.83 ± 12.13	0.59	0.96	0.49
5 min after intubation	120.45 ± 12.07	119.47 ± 12.66	0.97	0.22	0.72
7 min after intubation	119.78 ± 9.99	121.61 ± 12.81	0.86	0.16	0.51
After intubation	119.72 ± 10.33	119.45 ± 11.66	0.84	0.21	0.40

Table 4: Mean DBP at different pre-defined points of time

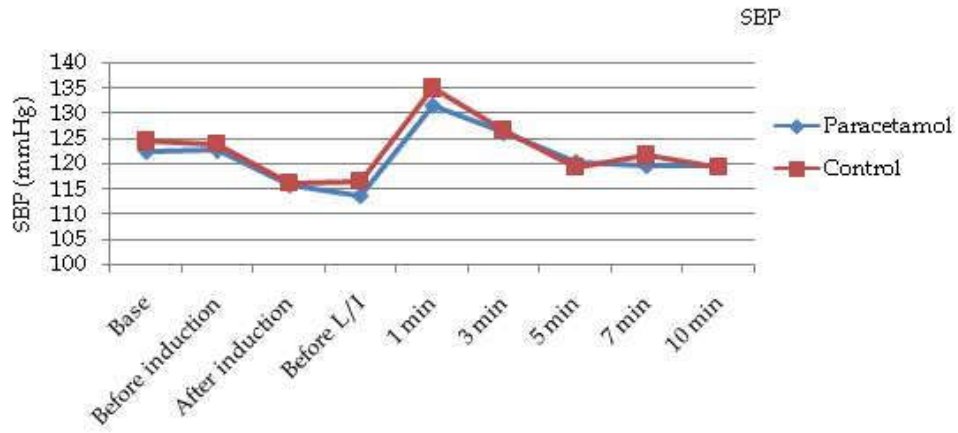
DBP			**Within Group**		**Inter Group**
	Group A	**Group B**	**Group A**	**Group B**	
	Mean ± SD	**Mean ± SD**	***p* - Value**	***p* - Value**	***p* - Value**
Baseline	76.01 ± 9.82	76.97 ± 11.12			0.13
Before induction	76.34 ± 11.41	77.85 ± 10.02	1.0	1.0	0.14
After induction	71.57 ± 9.32	73.21 ± 8.89	0.003	0.001	0.38
Before laryngoscopy	72.00 ± 10.84	72.92 ± 9.53	0.02	0.005	0.41
1 min after intubation	82.39 ± 10.95	86.27 ± 15.06	0.005	< 0.0001	0.38
3 min after intubation	77.74 ± 10.98	79.68 ± 12.72	0.98	0.86	0.42
5 min after intubation	74.47 ± 10.29	74.97 ± 9.83	0.99	0.97	0.10
7 min after intubation	74.37 ± 9.74	77.13 ± 10.87	0.99	1.0	0.13
10 min after intubation	73.26 ± 10.31	75.08 ± 10.38	0.79	0.98	0.24

DBP = Diastolic Blood Pressure; SD = Standard deviation.

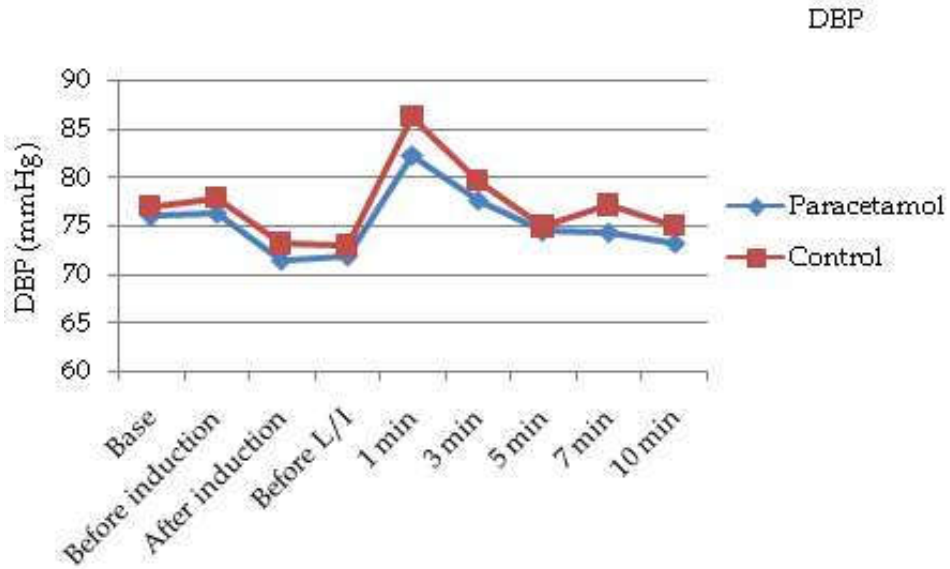
Table 5: Mean of MAP at different pre-defined points of time

MAP			**Within Group**		**Inter Group**
	Group A	**Group B**	**Group A**	**Group B**	
	Mean ± SD	**Mean ± SD**	***p* - Value**	***p* - Value**	***p* - Value**
Baseline	91.29 ± 11.03	92.77 ± 11.24			0.06
Before induction	91.49 ± 11.99	94.07 ± 10.65	1.0	0.9	0.11
After induction	86.24 ± 9.10	87.37 ± 8.53	0.002	0.001	0.37
Before laryngoscopy	86.01 ± 10.33	87.49 ± 9.35	0.002	0.007	0.19
1 min after intubation	99.26 ± 11.94	103.43 ± 15.53	< 0.0001	< 0.0001	0.55
3 min after Intubation	95.07 ± 11.31	96.57 ± 11.86	0.39	0.47	0.06
5 min after intubation	90.47 ± 10.24	90.85 ± 10.08	1.0	0.98	0.63
7 min after intubation	90.54 ± 8.25	91.76 ± 10.52	1.0	1.0	0.23
10 min after intubation	89.43 ± 9.49	91.05 ± 10.60	0.98	0.99	0.54

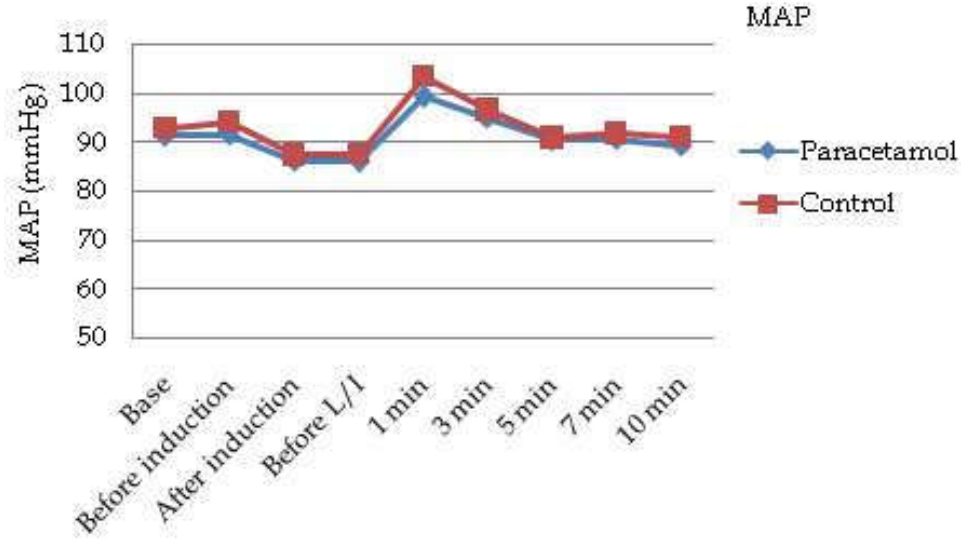
MAP = Mean Arterial Pressure; SD = Standard deviation.



Graph 1: Mean SBP of both the groups at different times



Graph 2: Graph showing the mean DBP of both the groups at different times



Graph 3: Showing intergroup MAP at different times

Discussion

Laryngoscopy and endotracheal intubation are the basis of protecting the airway in patients receiving general anesthesia. In addition to securing the airway, preventing aspiration and aiding delivery of anesthetic gases, they are also responsible for various stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure.[1] Several drugs have been used previously to attenuate these stress responses to the manipulation and stimulation of the airway during laryngoscopy and intubation. Fentanyl, beta-adrenergic receptors blockers, and lignocaine have all been used previously with varying results.[14]

In our study, we compared the efficacy of preoperative administration of intravenous paracetamol *1 gram* in *100 ml* volume on attenuation of hemodynamic responses after laryngoscopy and tracheal intubation. Patients of both the groups were premedicated with I.V. Fentanyl *1 mcg/kg*, as other no pharmacological agent was used to prevent hemodynamic response in any single patient undergoing laryngoscopy and intubation. The study was designed to evaluate the efficacy of paracetamol to attenuate the hemodynamic responses caused by the pain of laryngoscopy and endotracheal intubation.

Paracetamol has a well-established safety and analgesic profile. The main mechanism of action is inhibition of the enzyme cyclo-oxygenase, which is responsible for the production of prostaglandins, an important mediator of inflammation and pain.[15] The exact mechanism of paracetamol on hemodynamic responses is unclear but may be attributable to its analgesic effect mediated by its anti prostaglandin action.[16]

Although the peri-operative analgesic effects of intravenous paracetamol are well-known, literature documenting the attenuation of hemodynamic responses to laryngoscopy and intubation are very rare. Ali Kord Valeshabad *et al.* compared the prodrug of paracetamoli in 2 gram intravenous propacetamol with intravenouslidocaine *1.5 mg/kg* and found that propacetamol attenuated the heart rate responses to laryngoscopy but not the blood pressure responses to intubation.[13] Propacetamol [4-(acetamido) phenyl N, N-diethylglycinate] is a prodrug, which is quickly hydrolyzed by plasma esterase to vigorous paracetamol; *1 gr* propacetamol metabolized to *500 mg* paracetamol.[17] These findings were quite similar to our study. Our findings showed that preoperative administration of paracetamol did help attenuate the heart rate response to laryngoscopy and endotracheal intubation as compared to normal saline. However, paracetamol did not have any beneficial effect on attenuation of blood pressure responses to laryngoscopy and intubation. Acute increase in heart rate in their study was better attenuated than ours, which could be attributed to a higher dose of fentanyl (*2 mcg/kg*) used by them.

Ayatollahi V *et al.*, studied the effect of pre-operative administration of intravenous paracetamol during cesarean section on hemodynamic variables relative to intubation in 60 patients and observed that paracetamol prevented significant increase in SBP, DBP, MAP and HR at all times after laryngoscopy and intubation.[18] Hossam *et al.*, too evaluated the effect of *1 gram* of pre-operative intravenous paracetamol on hemodynamic variables after intubation in 60 obstetric patients planned for cesarean section and concluded that preoperative administration of intravenous paracetamol was effective in preventing hemodynamic responses to intubation.[19] In both the studies by Ayatollahi V *et al.* and Hossam *et al.*, opioids were not used before intubation as the patients were all obstetric cases. So, in the absence of opioids, probably the antinociceptive activities of paracetamol might have been augmented. However, another study by Ozmete *et al.* on the effect of pre-operative paracetamol on hemodynamic responses after intubation and its role on post cesarean delivery pain did not find any favorable effect on the hemodynamic variables following laryngoscopy and intubation.[20]

Thus, different studies have different opinions on the role of pre-operative paracetamol on attenuation of hemodynamic response to intubation. However, the context of these studies were not similar; in some studies opioids were used as premedication and in some they were not used. Hence, it may be recommended that further studies with similar context and larger sample sizes are carried out to find out the exact role of paracetamol among the pharmacological armamentarium available for blunting of hemodynamic responses.

Conclusion

Administration of paracetamol (*1 gram*), thirty minutes prior to induction of anesthesia could not totally blunt all the cardiovascular responses to laryngoscopy and intubation, but it did show better control of heart rate after intubation.

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A Comparative Study on the Endotracheal Tube Cuff Pressure Changes between Supine and Prone in Patients Undergoing Prone Position Surgeries

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Abstract

Background: The objective of the study was to compare the study on the endotracheal tube cuff pressure changes between *supine and prone* in patients undergoing prone position surgeries. *Materials and Methods:* After obtaining approval from institutional ethics committee, this study was conducted in Department of Anesthesiology at Sri Manakula Vinayagar Medical College and Hospital, Puducherry between *November 2015* and *August 2017*. A total of 60 patients who met the inclusion criteria were enrolled into study and prepared for General Anesthesia in prone position. After induction, the cuff pressure was recorded with head in neutral, flexed and extended position; these parameters were noted with patient in supine position and then in prone position. *Results:* There was no significant difference in mean cuff pressure at neutral posture between *supine* and *prone* position. Mean cuff pressure was increased after flexion and extension from neutral posture in both supine and prone position. At flexed posture mean cuff pressure was higher in supine position and at extended posture mean cuff pressure was higher in prone position. *Conclusion:* With this study we concluded that the supine or prone position has no influence on the cuff pressure when the head is in neutral position. In the supine position flexion of the head should be avoided because it leads to higher cuff pressure than with the head flexed in prone position. Similarly extension of the head should be avoided in the prone position.

Keywords: Cuff pressure; Supine position; Prone position.

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Introduction

Andreas Vesalius (1543) first experimented the idea of tracheal intubation by placing a reed into the trachea of a pig to treat a pneumothorax.[1,2] Benjamin Pugh (1754) performed the first endotracheal intubation to resuscitate a neonate with a leather covered coiled wire.[1] The main evolution of the endotracheal tube (ETT) is intertwined with that of surgery and anesthesia and, more recently, with critical care medicine. General anesthesia is one of the most common type of anesthesia practiced all over the world. Airway management by using a endotracheal tube (ETT) is the most important skill for a clinical anesthesiologist as it is an integral part of general anesthesia. The endotracheal tube cuff pressure is normally kept between *20 and 30 cm* of H_2O. Under inflation can cause air leakage

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because the glottis seal is inadequate and which lessens the effect of mechanical ventilation and produces a leakage of inhalation anesthetics, it may lead to micro aspiration and its an risk factor for ventilator associated pneumonia. However, over-inflation of the endotracheal tube cuff can cause a serious injury and affect blood flow to the tracheal mucosa, resulting in tracheal stenosis, tracheoesophageal fistula, or tracheal rupture. It is commonly associated with long procedures, these complications may occur even after a short duration of anesthesia. The tracheal intubated ETT can be displaced by movement of the patient's head and neck. Movement of the head and neck (rotation, flexion, and extension in the supine position) can cause displacement of endotracheal tube and change in endotracheal tube cuff pressure. Flexion may cause carina stimulation or endobronchial intubation by advancing the ETT, whereas extension can cause balloon-induced vocal cord damage or unintentional extubation by withdrawing the tube.[3] Although cuff pressures are checked initially after intubation, seldom it is done intermittently or continuously throughout operation. There are multiple peri-operative factors which may alter the ETT cuff pressure like usage of Nitrous oxide in anesthesia, inadequacy of muscle relaxation, surgical stimulation in cases of head and neck surgeries and change in patient position. This puts the patients for either micro aspiration or to the other extreme tracheal ischemic necrosis leading to tracheal stenosis. The purpose of the study is to compare the endotracheal tube cuff pressure changes between supine and prone positions in patients undergoing prone position surgeries.

Materials and Methods

After getting clearance from the institutional ethical committee and informed written consent from the study participants, a prospective observational study was conducted on 60 patients between the age group of *20* and *60 years* with ASA I, ASA II physical status undergoing elective surgeries under general anesthesia. Patients with ASA III and ASA IV physical status, Neck pain, previous history of neck surgery, limitation of neck movements, Morbid obesity (body mass index > 35) were excluded from the study.

Pre-anesthetic checkup was done a day prior to the surgery and the patient were kept fasting for *6* to *8 hours*. On the day before surgery the patient's received T Ranitidine *150 mg* in the night and at *7 AM* on the day of surgery along with T. Metoclopramide *10 mg*. The patient's were shifted to waiting room and again re-assesed. An intravenous line was secured using a 18 G venflon. Baseline monitors were attached and recorded (ECG, NIBP, SpO_2, $ETCO_2$ & Temperature). Anesthesia was induced by Inj. Glycopyrolate *0.01 mg/kg* I.V., Inj. Midazolam *0.05 mg/kg* I.V. followed by Inj. Fentanyl *2 mcg/kg* I.V., Inj. Propofol *2.mg/kg* I.V., then followed by Inj. Succinylcholine *2 mg/kg* I.V. and patient's were intubated with appropriate size flexometallic endotracheal tube and cuff were inflated by using air. Anesthesia was maintained with Inj. Vecuronium *0.08 mg/kg* I.V. and Sevoflurane following which the cuff pressure was monitored with patient in supine position with head in neutral position, flexion and extension. After the patient position changed from supine to prone once again the cuff pressure was monitored with patient in prone position with head in neutral position, flexion and extension.

Results

Sixty patients including 33 men and 27 women were assessed for endotracheal cuff pressure between supine and prone position. Demographic data are shown in (**Table 1**).

Table 1: Demographic data of the studied patients

Gender (Male/Female)	33/27
Patients age in years (Mean ± SD)	42.1 ± 9.8
BMI (Mean ± SD)	22.3 ± 2.6

Mean cuff pressure was increased after flexion and extension from neutral posture in both supine and prone position. At flexed posture mean cuff pressure were higher in supine position and at extended posture mean cuff pressure were higher in prone position. There were no differences between supine and prone in neutral, flexed and extended posture shows in (**Table 2**).

Table 2: Cuff pressure in Supine and Prone positions

Cuff pressure	Supine	Prone
	Mean ± SD	Mean ± SD
Neutral Posture	25.2 ± 2.3	24.8 ± 1.9
Flexed Posture	38.6 ± 3.2	37.5 ± 3.1
Extended Posture	41.1 ± 4.4	42.6 ± 4.0

There were no significant difference in mean cuff pressure between males and females in both supine and prone position shows in (**Table 3**).

Table 3: Difference in cuff pressure in Supine and Prone position between males and females

	Supine (Mean ± SD)		Prone (Mean ± SD)	
	Male	Female	Male	Female
Neutral Posture	24.8 ± 2.3	25.6 ± 2.3	25.1 ± 1.7	24.4 ± 2.0
Flexed Posture	39.0 ± 3.3	38.1 ± 2.9	37.1 ± 3.4	38.1± 2.8
Extended Posture	41.8 ± 3.8	40.2 ± 5.0	43.3 ± 3.2	41.6 ± 4.7
Supine Neutral to Flexion	36.0 ± 6.2	32.7 ± 7.5	31.9 ± 7.2	35.5 ± 7.3
Supine Neutral to Extension	40.0 ± 7.6	34.7 ± 17.3	41.8 ± 5.4	40.7 ± 6.7

Mean cuff pressure were lowest in neutral position and highest in extended posture in all the BMI groups. Mean cuff pressures in supine positions were highest in normal BMI subjects and lowest in underweight subjects shows in (**Table 4**).

Table 4: Mean cuff pressure comparison with respect to BMI in neutral, flexed and extended posture in supine and prone positions.

		BMI		
		< 18.5 (Underweight)	18.5 to 24.9 (Normal)	> 25 (Overweight)
		Mean ± SD	Mean ± SD	Mean ± SD
Supine	Neutral Posture	26.0 ± 2.8	25.1 ±1.9	25.1 ± 4.5
	Flexed Posture	36.0 ± 5.7	38.9 ± 2.4	37.1 ± 6.3
	Extended Posture	37.0 ± 9.9	41.4 ± 3.7	39.7 ± 7.4
Prone	Neutral Posture	26.0 ± 2.8	24.9 ± 1.6	23.7 ± 3.1
	Flexed Posture	39.0 ± 4.2	38.0 ± 2.9	33.7 ± 2.4
	Extended Posture	43.0 ± 4.2	42.9 ± 3.5	39.7 ± 6.5

Discussion

Trendelenburg (1869) is credited with designing the first inflatable cuff, which was a thin rubber bag fitted over the end of a tracheostomy tube, creating a tight seal to prevent aspiration during anesthesia.[4] Although the detachable inflatable cuff had been introduced by Trendelenburg, it had fallen out of favor due to technical issues, and clinicians preferred to use pharyngeal packing with sponges to seal the upper airway.

Guedel (1928) and Waters (1931) reintroduced the inflatable cuff to Magill's rubber tube and are credited with starting a period of ETT design.[5] Their first cuffs were made from the fingers of rubber gloves and from rubber condoms. These cuffs, ranging from *3* to *4 inches* long, were designed to sit half above and half below the glottis.[6] Later, they designed cuffs from rubber dental dams that were shorter, 1.5 inches long, and designed to sit below the vocal cords.[7]

Two modifications of the standard ETT were introduced commercially in the 1970s. One modification was to replace the standard pilot balloon with a larger balloon containing an inner pressure-regulating valve that maintains intra cuff pressure at *30 cm* H_2O.[8] Another modification was to replace the air-filled cuff with a self-inflating foam cuff in 1971 by Kamen and Wilkinson, it is known as the Bivona Fome-Cuff Tube.[9,10] Eisenmenger (1893) was the first to describe the use of a cuffed ETT, as well as the concept of a pilot balloon to monitor intra cuff pressure.[11]

Endotracheal tube cuff pressure monitoring is important to prevent serious complications like tracheal micro aspirations, inadequate delivery of inhaled anesthetics, aspiration pneumonia, bronchospasm, laryngospasm, tracheal stenosis, tracheoesophageal fistula, or tracheal rupture.

Normal endotracheal tube cuff pressure should be maintained between *20* and *30 cm* of H_2O to prevent above said complications. It is noted that endotracheal tube cuff pressure varies with varying head posture like neutral, flexion and extension in both supine and prone position. This study was conducted to know the changes in the endotracheal tube cuff pressure in different head postures and results are obtained.

In similar to our study, Christelle Lizy *et al.*, showed that there was a significant rise in endotracheal tube cuff pressure with change of position from supine neutral to supine extension and supine flexion.[12]

In similar to our study Deokkyu *et al.*, observed there were differences between *supine* and *prone* position for neutral, flexed, and extended angles. The initial neutral pressure increased after changing position from supine to prone. Flexed and extended pressure in supine was increased than the adjusted neutral pressure. Flexed and extended pressure in prone were increased than the adjusted neutral pressure.[3] In our study. we observed that endotracheal tube cuff pressure increases when the patient's position changed from supine neutral to supine flexion and supine extension.

In a study, done by Umeshkumar Athiraman *et al.*, showed that significant decline in endotracheal tube cuff pressure were found in the prone group from initial intubated supine position. These results were non-concurrent with our study, we observed that there is rise in endotracheal tube cuff pressure were noted in prone flexion and prone extension.[13]

In similar to our study, Armando Carios Franco de Godoy *et al.*, showed that change in body position can cause significant change in endotracheal tube cuff pressure. These results are comparable with our study where endotracheal tube cuff pressure were increased in both flexion and extension in supine and prone position.[14]

In similar to our study, Hiromi Kako *et al*., concluded that the significant changes in the intra cuff pressure occur with changes in head and neck position.[15]

In contrast to our study, Toshiyuki Minonishi *et al*., concluded that after the supine-to-prone position change, patients had ETT tube displacement. Such ETT movement may be accompanied by a decrease in cuff pressure. But in our study, we observed that there was no ETT displacement in supine to prone position. But endotracheal tube cuff pressure increases when the patient's position changed from prone neutral to prone flexion and prone extension.[16]

In similar to our study, Nobuyasu Komasawa *et al.*, concluded that there were cuff pressure increases with positional changes in head and neck flexion and extension. But in our study, we observed that at Flexed posture mean cuff pressure was higher in supine position and at extended posture mean cuff pressure was higher in prone position.[17]

In our study, we compared the changes in endotracheal tube cuff pressure by change in position by classifying the study objects based on their Body Mass Index (BMI). Our observation showed that there were no significant change in endotracheal tube cuff pressure in obese patient compared to normal and underweight patients. The changes were similar in both group, so we conclude that the change in Body Mass Index (BMI) has no impact in endotracheal tube cuff pressure.

Based on our observation we recommend that either in supine or prone position the head should be preferably placed in neutral position to avoid unwanted incidents like tracheal ischemic necrosis, stenosis due to pressure changes in cuff. We also advocate intermittent endotracheal tube cuff pressure monitoring is mandatory intra-operatively for the safety outcome of the patients.

Conclusion

The supine or prone position have no influence on the endotracheal tube cuff pressure when the head is in neutral position.

In supine position, flexion of the head should be avoided because it leads to higher cuff pressure than with the head flexed in prone position. Similarly extension of the head should be avoided in the prone position because it leads to higher cuff pressure.

Endotracheal tube cuff pressure have to be monitored and optimized during change of patients position from supine to prone position to prevent micro aspiration and mucosal damage of airway.

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Comparison of Bolus Doses of Bronchodilator and Adrenergic on Intra-operative Hypotensive Episodes throughout Caesarean beneath Spinal Anesthesia

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Abstract

Background: The present study was designed to check the vasoconstrictive effects of bronchodilator and adrenergic in bettering cardiovascular disease in elective cesarean receiving crystalloid coloading throughout intrathecal bupivacaine injection. *Material and Methods:* 30 patients were selected in present study. Once pre-anesthetic analysis and investigations, the patients were explained regarding the procedure. Cluster E were received blood vessel (IV) bronchodilator five mg and cluster P were received blood vessel (IV) adrenergic a hundred weight unit once there'll be fall in maternal pulse force per unit area (SBP) > 20% from the bottom line. *Results:* The two teams, i.e., cluster one and cluster a pair of matched with relation to their age, weight and height. Overall, 7/15 (46.66%) patients within the adrenergic cluster and 7/15 (46.66%) patients within the bronchodilator cluster had one or additional episode of cardiovascular disease and needed one or additional bolus of vasoconstrictive. Compared with the baseline values, the amendment in mean rate among completely different intervals were found to be non-vital at any given time interval ($p > 0.05$). *Conclusion:* We conclude from the current study that bronchodilator five mg and adrenergic a hundred µg square measure equally economical in managing cardiovascular disease throughout spinal for cesarean.

Keywords: Bronchodilator; Adrenergic; Spinal Anesthesia; Cesarean Section.

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Introduction

Spinal anesthesia (SA) is today thought-about the quality anesthetic technique for elective cesarean.[1] However, cardiovascular disease is that the commonest aspect result of neuroaxialblocks within the medicine patient. Spinalfor cesarean is relatedto eightieth of cardiovascular disease cases while not prophylactic measures.[2]

Spinal cardiovascular disease will occur sharply and, if severe, may end up in vital perinatal adverse outcomes, like maternal nausea and ejection, vertigo craniate pathology and should be a vital tributary issue for maternal death associated with anesthesia.

Mothers with pre-delivery hypovolemia is also in danger of vessel collapse as a result of the sympathetic blockade could severely decrease blood vessel come back. Profound cardiovascular

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disease will probably result in serious drive and hypovolemia within the mother and therefore the vertebrate. As placental blood flow is directly proportional to the maternal force per unit area, the cardiovascular disease will result in to placental hypoperfusion and craniate physiological state leading to explained less craniate activity and cranial pathology.

So, hindrance of spinal cardiovascular disease has been a key analysis space at intervals the sphere of medicineanesthesia. To prevent spinal cardiovascular disease, variety of approaches is investigated like girdle tilt, leg elevation and wrapping, and therefore the prophylactic administration of fluids or vasopressors that square measure accustomed cut back the incidence of maternal cardiovascular disease. The utilization of vasopressors has gained increasing prominence because the primary technique for the hindrance and treatment of spinal cardiovascular disease throughout cesarean.[3]

There is a trend to bank additional on vasopressors than either crystalloid or mixture alone. Crystalloid pre-hydration has poor effectivity for preventing cardiovascular disease, in all probability as a result of it undergoes speedy distribution. As an alternate, speedily administering crystalloid at the time of initiation of physiological condition (called coloading) is also additional physiologically applicable because the most result may be achieved throughout the time of block and resulting dilation evolution. Completely different vasopressors square measure unremarkably used now-a-days with varied degrees of success. Despite the utilization of prophylactic blood vessel (I.V. infusion or bolus bronchodilator for the last 3 decades, a good range of failures have additionally been reportable.[4]

Ephedrine has beenthe vasoconstrictive of selection since it's been shown to own a additional protecting result on female internal reproductive organ blood flow and introduction pressure than α-adrenergic agonists.[5] However, bronchodilator is not any longer the old normal for prevention and treatment of cardiovascular disease once spinal for cesarean. Moreover, higher dose of bronchodilator causes vital maternal cardiac arrhythmia and cranial pathology.[6]

Newer proof has supported the utilization of alpha gonists like adrenergic demonstrating higher acid base standing and similar effectivity in force per unit area management. Hence, the current study was designed to check the vasoconstrictive effects of bronchodilator and adrenergic in bettering cardiovascular disease in elective cesarean receiving crystalloid co-loading throughout intrathecal bupivacaine injection.

Materials and Methods

The analysis of "Comparison of bolus doses of bronchodilator and adrenergic on intra-operative hypotentive episodes throughout cesarean beneath spinal anesthesia" were allotted within the Department of Anesthesiology, Saraswathi Institute of Medical Sciences, Anwarpur, Hapur, Uttar Pradesh, India.

Inclusion Criteria

- ASA I and II denote for elective caesarean.
- All the patients WHO square measure willing to grant consent.
- Age cluster eighteen to *thirty five years*.
- Weight *40–70 kg*.
- Height *one hundred fifty –160 cm*.

Exclusion Criteria

1. Patients not willing to grant consent.
2. Patients WHO have a past history of reaction to review medicine, major viscus, excretory organ or vessel dysfunction and any reason to central neuraxial blockade.
3. Patients having allergic to native anesthetics.
4. Patients having trauma coagulopathy.
5. Patients WHO were taking anti-emetic medication.
6. Fat patient.
7. Patients with physiological condition connected complications like vertebrate malpresentation, pregnancyinduced high blood pressure, physiological state diabetes and pts with pre-toxemia of pregnancy and toxemia of pregnancy.

Methods

30 patients were selected in present study. Once pre-anesthetic analysis and investigations, the patients were explained regarding the procedure, sophisticated written consent was obtained. normal pre-operative procedure was followed and final analysis important parameters were recorded. 18 G IV tube were secured and allotted

into 2 teams of fifteen every with pc generated information. cluster E were received blood vessel (IV) bronchodilator *five mg* and cluster P were received blood vessel (IV) adrenergic a hundred weight unit once there'll be fall in maternal pulse force per unit area (SBP) > 20% from the bottom line. In the operation theatre, routine monitors (electrocardiogram, non-invasive force per unit area, pulse oximeter), blood vessel access was secured. All the patients were co-loaded with Ringer wet-nurse *20 ml/kg*.

Spinal was given twenty three G Quincke needle in sitting position at the L3-L4 interspace. Once the free flow of humour (CSF) is obtained, *2ml* (*10 mg*) of zero. 5% Bupivacaine (heavy) were administered over zero. *2ml/sec.* Co-loading with speedy administration of *20ml/kg* of Ringer wet-nurse were started. Patients can then be placed within thesupine position, activity got via a Hudson mask at the speed of *three l/min*.

Sensory block were assessed by a pinprick take a look at. The onset of sensory blockade (defined because the time from the injection of intrathecal medicine to the absence of pain at the T8 surgical instrument were recorded each minute until the T8 level is achieved. Onset of motor blockade were assessed at *5-min* intervals until *fifteen min* (*i.e.,* B5, B10 and B15) per the changed.

Bromage scale [0 - no motor block, one - inability to flex the hip [hip blocked], a pair of - inability to flex the knee [hip and knee blocked], three - inability to flex the articulation talocrural is [hip, knee and articulation talocrural is blocked]), shows in (**Table 1**).

Table 1: Sedation Scale: Sedation will be assessed by Ramsey Sedation Scoring

Level 1	Patient anxious and agitated or restless, or both
Level 2	Patient co-operative, oriented, and tranquil
Level 3	Patient responds to commands only
Level 4	Brisk response to a light glabellar tap or auditory stimulus
Level 5	Sluggish response to a light glabellar tap or auditory stimulus
Level 6	No response to stimuli mentioned in items 4 and 5

Blood pressure (systolic, beat and mean), heart rate, rate of respiration and peripheral gas saturation (SpO_2) are going to be recorded five min before the intrathecal injection (0) and at five, 10, 15, 20, twenty five and thirty min once the injection, and after each fifteen min. Arrhythmia (defined as rate of but 50) are going to be treated with blood vessel zero. *6 mg* spasmolytic sulphate. Patients also will assessed for side-effects like nausea, vomiting, cardiovascular disease, arrhythmia, itching, abnormality.

Statistical Analysis

All the information were expressed as mean + American state, applied mathematics analysis were performed with SPSS version 17.0 for analysis of demographic comparison of teams, x_2, unmatched student's *t*-test and paired-*t*-test were applied. $p < 0.05$ were thought-about as statistically vital.

Results

The two teams, *i.e.*, cluster one and cluster a pair of matched with relation to their age, weight and height shows in **Table 2**. Overall, 7/15 (46.66%) patients within the adrenergic cluster and 7/15 (46.66%) patients within the bronchodilator cluster had one or additional episode of cardiovascular disease and needed one or additional bolus of vasoconstrictive. the amount of rescue doses needed in cluster one and cluster a pair of was statistically insignificant shows in **Tables 3 and 4**. There was the next incidence of arrhythmia in patients receiving adrenergic than those receiving bronchodilator shows in **Table 4**.

The comparison of mean of rate in numerous interval in between teams. Compared with the baseline values, the amendment in mean rate among completely different intervals were found to be non-vital at any given time interval ($p >$ zero.05) as shown in table on top of and shows the similar trends in between teams. Intra-operatively there was no arrhythmia recorded in each teams at any given interval. But the distinction in SpO_2 wasn›t found be statistically vital among completely different study teams at any given time intervals ($p > 0.05$) shows in **Table 5**. The distinction in birth weight of neonates between the 2 teams was statistically insignificant. No neonatal had Apgar score shows in **Table 6**.

Table 2: Demographic data of Groups E and P

	Group E (*n* = 15)	**Group *p* (*n* = 15)**	***p* - value**
Age (*years*)	30.17 ± 0.49	31.13 ± 0.51	0.58
ASA i:ii (*n*)	14:1	13:2	0.42
Weight (*kg*)	60.25 ± .80	68.26 ± 8.61	0.06
Height (*cm*)	153.29 ± 4.77	152.39 ± 5.23	0.51

n = Number of patients

Table 3: Heart rate recordings during various stages of anesthesia

Heart Rate	Group E	Group P
0 Minutes	79.20 ± 16.01	77.57 ± 14.40
5 Minutes	79.80 ± 11.47	75.57 ± 8.472
10 Minutes	81.97 ± 9.750	76.60 ± 11.83
15 Minutes	87.37 ± 6.990	84.20 ± 7.599
20 Minutes	86.37 ± 7.299	81.83 ± 10.95
25 Minutes	86.00 ± 10.00	80.50 ± 11.40
30 Minutes	86.60 ± 8.261	82.73 ± 8.081
45 Minutes	81.03 ± 10.36	77.23 ± 12.53
60 Minutes	85.07 ± 7.565	85.97 ± 11.43
75 Minutes	86.97 ± 6.990	83.63 ± 6.744
90 Minutes	86.37 ± 7.850	84.10 ± 20.50

Table 4: SpO_2 recordings during various stages of anesthesia

SpO_2	Group E	Group P
0 Minutes	98.33 ± 1.241	98.30 ± 1.512
5 Minutes	97.90 ± 1.322	98.23 ± 1.135
10 Minutes	98.00 ± 1.486	98.27 ± 1.285
15 Minutes	97.07 ± 1.639	97.77 ± 1.278
20 Minutes	97.57 ± 1.524	97.77 ± 1.775
25 Minutes	97.63 ± 1.691	98.03 ± 1.629
30 Minutes	97.67 ± 1.583	98.17 ± 0.9129
45 Minutes	97.60 ± 1.734	98.10 ± 1.373
60 Minutes	98.23 ± 1.524	98.17 ± 1.053
75 Minutes	97.57 ± 1.675	97.83 ± 1.487
90 Minutes	97.47 ± 1.655	98.10 ± 1.494

Table 5: Comparison of parameters in between groups

Parameters	Group E (n = 15) (%)	Group P (n = 15) (%)	p - value
Hypotension (yes)	7 (46.66%)	7 (46.66%)	1.00
Hypotension (no)	8 (53.33%)	8 (53.33%)	
Bradycardia	0	2 (13.33%)	0.01
Nausea/Vomiting	4 (26.66%)	6 (40%)	0.15
Tachycardia	3 (20%)	4 (26.66%)	0.75

Table 6: Apgar score of the two groups at different time intervals

Parameters	Group E (n = 15)	Group P (n = 15) (%)	p - Value
APGAR (*0 min*)	7.73 ± 0.39	7.69 ± 0.41	0.767
APGAR (*1 min*)	9.11 ± 0.41	8.97 ± 0.49	0.252
APGAR (*5 min*)	9.08 ± 0.32	8.95 ± 0.31	0.249
Baby weight (*kg*)	3.068 ± 0.322	3.163 ± 0.334	0.781

Discussion

In the gift study, there was no statistically vital distinction within the incidence of cardiovascular disease with speedy administration of crystalloid at the time of induction of spinal (coload) in each the teams (p > 0.05). Moreover, the general incidence of cardiovascular disease within the study population was forty eighth that was considerably less compared to the incidence (more than 80%) discovered in alternative studies.[2]

In this study, there was the next incidence of arrhythmia in patients receiving adrenergic than those receiving bronchodilator, this can be expected to ensue to extend in force per unit area with associate degree α-agonist which may result in reactive arrhythmia (baroreceptor reflex). However, this was tuned in to glycopyrollate while not adverse consequences. The results of this study is in accordance with the studies of Nazir *et al*.[7] (5/50 *vs* 17/50 within the adrenergic group) and Lee *et al*.[8] [relative risk (RR) of four 79; ninety fifth confidence interval (CI), 1.47–15.60] with p < 0.05. On the opposite hand, the incidence of nausea and ejection was additional within the adrenergic cluster than the bronchodilator cluster 14/40 (35%) versus 9/40 (22.5%) in our study that wasn't statistically vital (p = 0.16).

In our study, the common vasoconstrictive consumption was reduced within the bronchodilator cluster compared to the adrenergic cluster, assumptive that the equivalent doses of bronchodilator and adrenergic were *five mg* and a *hundred µg*, severally.[9] The incidence of fall in force per unit area was most throughout the primary ten min following the sub-arachnoid block and that we discovered that vasoconstrictive use was most throughout this era. This corresponds to the immediate sympathetic block once intrathecal injection. We tend to additionally discovered that adrenergic was used additional of times in ten min compared to bronchodilator. It's clearly apparent by the broader SDs of mean SBP values within the adrenergic cluster however no applied mathematics vital distinctionwas discovered (p > 0.05). On the opposite hand, Ngan Kee *et al.*[10] and Skilled worker *et al.*[11] opined that vasoconstrictive needs was reduced until the time of delivery in their studies. The common median dose was zeromg versus *ten mg* of bronchodilator (p < 0.001) within the study by Ngan Kee *et al.*[10]

Gunda *et al.*[12] compared the effectiveness and aspect effects of vasopressors bronchodilator and adrenergic administered for cardiovascular disease throughout cesarean beneath spinal. However, their study advised that adrenergic is also the additional applicable vasoconstrictive once considering maternal well-being. This could are because of less dose of bronchodilator (*3 mg*) that was utilized in their study as compared with this study.

Conclusion

We conclude from the current study that bronchodilator *five mg* and adrenergic a *hundred µg* square measure equally economical in managing cardiovascular disease throughout spinal for cesarean. Maternal arrhythmia was additional within the adrenergic cluster and there was no distinction within the incidence of cranial pathology within the 2 groups. Neonatal outcome remains equally smart in each the teams.

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Original Research Article

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Prevention of Post-operative Nausea and Vomiting in Laparoscopic Cholecystectomy: A Comparison of Metoclopramide and Ondansetron

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Abstract

Background: Post-operative nausea and vomiting (PONV) is a frequent complication associated with laparoscopic cholecystectomy. In this randomized double-blind placebo controlled prospective study, we compared the efficacy of intravenous metoclopramide and ondansetron for prevention of PONV following laparoscopic cholecystectomy in patients. *Materials and Methods:* A total of 75 patients (*20–60 years of age*) undergoing elective laparascopic cholecysetectomy were randomly allocated to one of the three groups of 25 patients each. Group A received metoclopramide *10 mg*, Group B received ondansetron and group C received normal saline *10 ml* after induction. All episodes of PONV within 24 hrs. after induction of anesthesia were recorded. *Results:* The overall incidence of post-operative emesis was 44% in control group, 16% in Metoclopramide group and 12% in Ondansetron group.The decrease in incidence of emesis in Metoclopramide and Ondansetron group was significant as compared to control group whereas there was no statistical difference between Metoclopramide and Ondansetron groups. *Conclusion:* For prevention of PONV after laparoscopic cholecystectomy, both metoclopramide and ondansetron are equally effective in comparison to placebo group.

Keywords: Laparoscopic cholecystectomy; Ondansetron; Metoclopramide; Post-operative nausea and vomiting.

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Introduction

Post-operative nausea and vomiting (PONV) has been one of the most distressing accompaniments of surgery and anesthesia, with an incidence of approximately 30%.[1] However, a higher incidence rate of 46% to 75% has been reported in patients after laparoscopic cholecystectomy.[2–4] This has been attributed tomechanical factors like pressure on the stomach and gut due to pneumoperitoneum as well as chemical factors like influence of carbon dioxide. Although nausea and vomiting can result in dehydration, electrolyte imbalances and delay in discharge from hospital but for the anesthesiologists, the most dreaded complication is the pulmonary aspiration of vomitus especially when airway reflexes are depressed due to the residual effects of anesthetic drugs.

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Various drugs and techniques have been employed in the past for the prevention of PONV but the search for better anti-emetics is still going on.[5,6] Metoclopramide is the routine drug being used for prevention of PONV for the last *30 years* due to its various favorable properties.[7] The anti-emetic action of metoclopramide is due to the antagonism of D_2 receptors centrally and peripherally. The inhibition of chemoreceptor trigger zone (CTZ) in the central nervous system prevents nausea and vomiting triggered by many stimuli. It also exhibits a gastrokinetic effect by increasing selective cholinergic response of gastrointestinal tract by inhibiting gastric smooth muscle relaxation. The tone of lower oesophageal sphincter is also increased thus decreasing the risk of aspiration. However, higher doses can lead to extrapyramidal side effects. In the recent years, interest has been focused on a new $5HT^3$ receptor specific antagonist, Ondansetron which does not act on other receptors like dopaminergic, histaminic, cholinergic etc. and so has few side effects.[8]

Therefore, this study was planned to evaluate the effectiveness of ondansetron and metoclopramide in preventing PONV in patients undergoing laproscopic cholecystectomy.

Materials and Methods

This study was carried at Government Medical College in Punjab after obtaining approval from ethical committee. The study was conducted on 75 adult patients of both sexes in age group of *20–60 years* of ASA grade I and II undergoing elective laparoscopic cholecystectomy. Before enrolment to the study, awritten informed consent was obtained from patients. Criteria for exclusion were obese patients (> 20% expected body weight for their age), patients with history of motion sickness, chronic steroid therapy or having had anti-emetics within last *24 hours* before surgery. Patients with chronic exposure to nicotine and having any disease that could prolong gastric emptying or make them prone to vomiting *e.g.*, diabetes, hiatus hernia were not included in the study.

Random allocation was decided on the basis of computer generated random number table. The coded slips were prepared and put in envelop and according to the slip, solution was prepared by independent observer not taking part in study.

Group A (n = 25) received injection metoclopramide *10 mg* I.V. diluted to make volume of *4 ml*.

Group B (n = 25) received injection ondansetron *4 mg* I.V. diluted upto *4 ml*. Group C (n = 25) received *4 ml* normal saline.

All the patients were subjected to a thorough pre-anesthetic checkup a day prior to surgery and relevant investigations were done. The patients were given tablet Diazepam *10 mg* on the night before surgery. After bringing patient to the O.T, I.V. cannula was placed and monitors were attached. Inj. Butorphanol *1 mg* and inj. Atropine *0.6 mg* were used for intravenous (I.V.) pre-medicantion. All patients were induced with inj. Thiopentone *5 mg/kg* and suxamethnoium *2 mg/kg* I.V. The study drug was given soon after intubation. During IPPV using bag and mask ventilation, low airway pressures were maintained.

Anesthesia technique employed was same in all patients using halothane, nitrous oxide, oxygen and vecuronium. Before extubation, patients received Inj. Diclofenac *75 mg* intra-muscularly.

Intra-operatively, continuous monitoring of patient's heart rate and blood pressure were done. Post-operatively, patients were monitored every hour for the first *4 hours* and then at *24 hours*. All episodes of nausea and vomiting were recorded during first *24 hours* after general anesthesia. Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit, whereas vomiting was defined as the forceful expulsion of gastric contents from the mouth. Any side effects of the drugs were also recorded.

Nausea was measured by 11 points numerical visual analog scale with 0 = no nausea and 10 = nausea as bad can be. A score of more than 5 was considered severe, 5 = moderate and 4 or less was considered minimal. Moderate or severe nausea was considered as major nausea. The numbers of vomiting episodes were counted and more than 2 episodes were counted severe, 2 episodes as moderate and less than 2 considered mild vomiting. Patients who had more than 2 episodes of vomiting were given inj. Metoclopramide *10 mg* I.V. as a rescue anti-emetic.

Results

All the 75 patients, 25 in each group were included in the study. There were no significant differences between the three groups with regard to age, weight and duration of surgery as shown in (**Table 1**). Intra-operative vital score was 1.88 ± 0.33, 1.92 ± 0.28 and 1.84 ± 0.37 in group A, B and C respectively. This was statistically in-significant. The post-operative

vital scores were almost similar in all groups. At no time, difference in the post-operative vital score was significant between the groups as shown in (**Table 2**). Nausea was experienced by 17 patients of control group (68%) while it was reported in 8 patients of Metoclopramide group (32%) and 9 patients of Ondansetron group (36%) respectively displays (**Fig. 1**). The mean maximum nausea severity score was 1.68 ± 2.97 in the metoclopramide group, 1.68 ± 2.98 in the ondansetron group and 4.28 ± 3.92 in the control group shows (**Table 3**). This difference was statistically significant between control versus (*v/s*) metoclopramide group ($p < 0.05$) and control *v/s* ondansetron group ($p < 0.05$) but statistically in-significant on comparison of metoclopramide *v/s* ondansetron groups ($p > 0.05$). In our study, metoclopramide was found to be more effective in decreasing severity of early nausea (0–2 hours) while ondansetron proved better as far as control of late nausea (2–24 hours) was concerned as shown in (**Tables 4 & 5**).

Table 1: Patient characteristics

Variables Mean ± SD	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)
Age (y) ± SD	39.96 ± 10.69	40.36 ± 7.78	39.08 ± 9.42
Weight (kg) ± SD	63.16 ± 9.47	64.26 ± 11.20	63.48 ± 10.61
Duration of surgery (min)	56.00 ± 13.69	57.40 ± 14.44	53.60 ± 12.71

Table 2: Mean vital scores

	Group A	Group B	Group C
IVS	1.88 ± 0.33	1.92 ± 0.28	1.84 ± 0.37
PVS-0HR	1.84 ± 0.37	1.92 ± 0.28	1.92 ± 0.28
PVS-1HR	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
PVS-2HR	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
PVS-3HR	2.00 ± 0.00	1.96 ± 0.20	2.00 ± 0.00
PVS-4HR	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
PVS-4-24HR	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00

IVS-Intra-operative vital score; PVS-Post-opeartive vital score; HR-Hour.

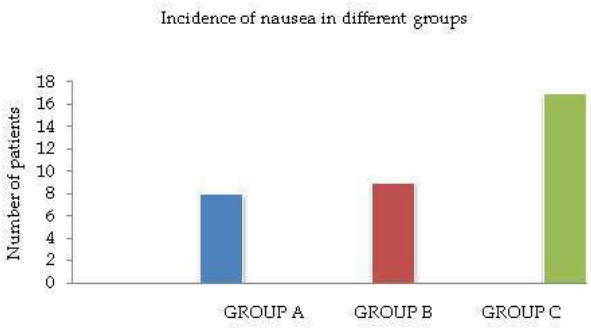

Fig. 1: Incidence of nausea in different groups

Table 3: Post-operative nausea score at different time intervals

Time (Hours)	Group		
	Metoclopramide	Ondansetron	Control
0	0.12 ± 0.44	0.08 ± 0.28	0.24 ± 0.52
1	0.56 ± 1.19	0.72 ± 1.24	1.04 ± 1.21
2	1.32 ± 2.46	1.04 ± 2.17	2.68 ± 2.69
3	1.48 ± 2.90	1.08 ± 2.63	2.96 ± 3.35
4	0.44 ± 0.92	0.72 ± 2.21	1.76 ± 3.28
4–24	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Max. Mean Severity Score	1.68 ± 2.97	1.68 ± 2.98	4.28 ± 3.92

The overall incidence of post-operative emesis was 44% in control group (11/25), 20% in Metoclopramide group (5/25) and 12% in Ondansetron group (3/25) (**Fig. 2**). The decrease in incidence of emesis in Metoclopramide and Ondansetron group was significant as compared to control group whereas there was no statistical difference between Metoclopramide and Ondansetron groups. However, during early period (0–2 hours) the incidence of vomiting was 4% in metoclopramide group as compared to 12% in both ondansetron and control group while it increased to 20% in metoclopramide and 40% in control group as compared to 8% in ondansetron group during late period (2–24 hours). No significant untoward side effects were seen in any of the three groups as

Table 4: Post-operative emesis at different time intervals

Time (Hours)	Group								
	Metoclopramide			Ondansetron			Control		
	No.	%	Mean	No.	%	Mean	No.	%	Mean
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	1	4	0.04 ± 0.20	3	12	0.12 ± 0.33	3	12	0.12 ± 0.33
3	4	16	0.16 ± 0.47	2	8	0.08 ± 0.28	8	32	0.32 ± 0.48
4	4	16	0.16 ± 0.37	2	8	0.08 ± 0.28	10	40	0.40 ± 0.71
4–24	1	4	0.04 ± 0.20	1	4	0.04 ± 0.20	5	20	0.20 ± 0.50

Metoclopramide *v/s* ondansetron - not significant;

Control *v/s* metoclopramide - not significant;

Control *v/s* ondansetron - highly significant at *3 hours and 4 hours.*

shown in (**Table 6**).Use of rescue treatment shown in (**Fig. 3**) was similar in metoclopramide and ondansetron group (8%) while it was was higher in control group (24%).

Table 6: Incidence of side effects

	Headache	Dryness of mouth	Sedation	Any other
Group A	1	1	1	1
Group B	2	2	0	1
Group C	1	2	0	1

Discussion

Despite scientific advances in anesthesia and surgery, nausea and vomiting are among the most common distressing post-operative complications. The etiology of PONV after laparoscopic cholecystectomy is multifactorial. Anesthetic factors like the type of pre-medication, amount of gastric distension, suctioning, anesthetic drugs, anesthetic technique and post-operative pain increase the incidence of PONV. Various non-anesthestic factors like age, gender, weight, history of motion sickness, anxiety, gastroparesis etc. also pre-dispose patients to PONV.[9] In our study, patients were similar in terms of demographic variables, duration of surgery and basic vital signs. Patients with low threshold for vomiting like gastroparesis, motion sickness etc. were excluded from our study. Anesthetic drugs and the technique used were kept similar in all groups.

In the present study, the overall incidence of nausea was 68% in control group while it was 32% in metoclopramide group and 36% in ondansetron group which was statistically in-significant

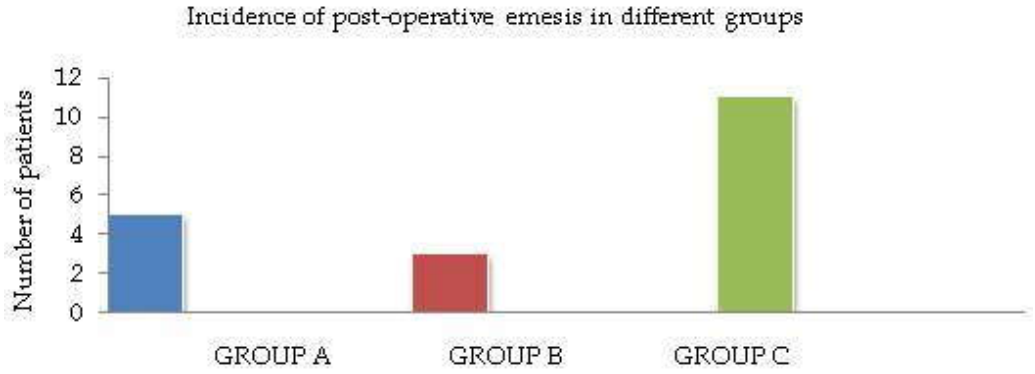

Fig. 2: Incidence of post-operative emesis in different groups

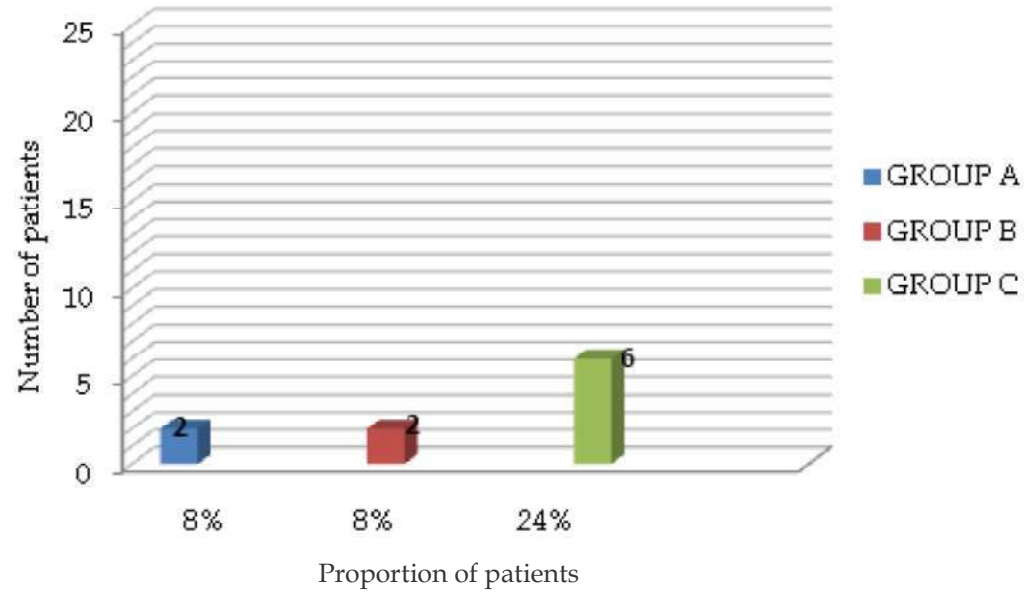

Fig. 3: Incidence of use of rescue treatment in different groups

amongst metoclopramide and ondansetron group but signifant for both groups in comparison with control group. Incidence of post-operative emesis was 44% in control group (11/25) which was significant ($p < 0.001$) when compared to 20% in Metoclopramide group (5/25) and 12% in Ondansetron group (3/25) thus showing that the incidence of post operative vomiting was maximum in control group. As per our results, the frequency of emesis was less in the ondansetron group but it was not statistically significant when compared to the metoclopramide group. These results are in concordance with the studies by Wilson *et al.* and Bilgin TE *et al.* who proved a significant decrease in the incidence of vomiting in the ondansetron and metoclopramide groups as compared to the control group without any statistical difference amongst themselves.[10,11] K Isazadehfar[12] concluded that both metoclopramide and ondansetron are equally effective for prevention of vomiting butfor prevention of nausea, ondansetron is more effective than metoclopramide.

In a similar research, Quanyor and Raedar showed the overall incidence of post-operative nausea and vomiting to be almost similar in metoclopramide and ondansetron groups. Incidentally, they also observed a greater incidence of moderate to strong pain during the post-operative period in the ondansetron group as compared to the metoclopramide group.[13]

Farhat K *et al.* on the other hand, stated that the frequency of nausea and vomiting was clinically and statistically lower in ondansetron group as compared to the metoclopramide group ($p = 0.035$) while the use of rescue anti-emetic was significantly higher in the latter ($p = 0.022$).[14] These findings were also reinforced in a meta analysis by Wu SJ *et al.*, where the total incidence of post-operative nausea and vomiting within 24 hours after laparoscopic cholecystectomy was 31% in the ondansetron group and 56% in the metoclopramide group thus indicating ondansetron to be a better anti-emetic.[15]

In the present study, we found the incidence of 'early nausea' to be 28% and 36% in metoclopramide and ondansetron group respectively as compared to 64% in control group. The incidence of 'late nausea' was 32% for metoclopramide group, 24% for ondansetron group and 60% for control group. Thus it shows that ondansetron is more effective for 'late nausea' than metoclopramide. It also decreases severity of 'late nausea' as compared to Metoclopramide. The decreased effect of metoclopramide on 'late nausea' may be due to its shorter duration of action. Masoomeh Tabari *et al.*[16] in their study concluded that Ondansetron was more effective than dexamethasone and metoclopramide in preventing vomiting after laparoscopic cholecystectomy at intervals of *0–1* and *1–6 hours* and also delayed the onset of nausea and vomiting.

Many studies reported that ondansetron is statistically superior to metoclopramide for prevention of PONV.[17–19] In our study too, ondansetron group has low frequency of emesis although it was statistically insignificant. Other published studies that evaluated the efficacy of ondansetron and metoclopramide administered intravenously have shown similar reductions in the incidence of PONV during the *24 hrs.* post recovery period.[20,21] Though we encountered very few and mild side effects with regard to all groups, Daria and Kumar stated that metoclopramide not only has a low (36.7%) success rate in the prevention of PONV, but also a higher incidence of side effects. However, they also discredited the efficacy of ondansetron for the prevention of PONV.[22]

Conclusion

Ondansetron *4 mg* and metoclopramide *10 mg* are both almost equally effective as prophylactic anti-emetics for the prevention of post-operative nausea and vomiting in laparoscopic cholecystectomy procedures under general anesthesia as compared to placebo with minimal side effects.

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Original Research Article

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Study of Clonidine vs Fentanyl Intrathecally with 0.5% Bupivacaine in Vaginal Hysterectomy: A Comparative Study

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Abstract

Bupivacaine is the most common drug used in spinal anesthesia in vaginal hysterectomy which gives adequate anesthesia for the procedure. Clonidine is α2 agonist used to prolong the duration of intrathecally administered local anesthetic and has potent antinociceptive properties. Fentanyl not only improves the quality of intra-operative analgesia but also reduces the need of supplemental sedation. In the present study, we tried to find out whether quality of of anesthesia is better with low dose bupivacaine and clonidine or with low dose bupivacaine and fentanyl. *Methods:* Prospective, randomised double-blind, controlled study was conducted in a tertiary care institution. 80 patients ASA Grade I and II scheduled for vaginal hysterectomy were randomly allocated into two groups by using computer generated random numbers. Group BC (n = 40) received 0.5% Hyperbaric bupivacaine 2.8 ml (14 mg) + 25 mcg Clonidine and Group BF (n = 40) received 0.5% hyperbaric bupivacaine 2.8 ml (14 mg) + 30 mcg Fentanyl intrathecally. Time for onset of sensory and motor blockade, time to achieve maximum sensory and motor blockade, time for segment regression up to L1, side effects, peri-operative and post-operative analgesic requirements were assessed. *Results:* Mean duration of onset to peak sensory block (5.45 ± 0.50 min), onset to peak motor block (7.05 ± 0.22 min) was significantly higher in group BC as compared to group BF (6.90 ± 0.38 min) and (8.67 ± 0.47 min) respectively. Significant difference in mean duration of sensory block and motor block (189.80 ± 6.49 min, 247.28 ± 8.42 min) in group BC and group BF (150.23 ± 4.23, 197.08 ± 6.25 min) were noted. Duration of post-operative analgesia was significantly higher in group BC (495.93 ± 22.43 min) as compared to group BF (269.33 ± 17.98 min). There was significant difference between VAS score in group BC and group BF except 4th hr and 18th hr. All patients were hemodynamically stable and no significant difference in post-operative sedation and adverse effects was observed. *Conclusion:* Clonidine and fentanyl are good adjuvant drugs and their use intrathecally as an additive to bupivacaine extends the duration of spinal anesthesia significantly, lowering the need to administer general anesthesia if duration of surgery is prolonged. Further they also provides excellent post-operative analgesia. Clonidine is better adjuvant with bupivacaine in view of better sensory and motor blockade, prolonged post-operative analgesia.

Keywords: Clonidine; Fentanyl; Analgesia; Vaginal hysterectomy.

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Introduction

Pain, one of the most dramatic, complex and universal phenomenon is defined as "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Post-operative pain is associated with various systemic adverse responses all contributing to increase post-operative morbidity and mortality. Hence, an effective pain relief after surgery is essential for optimal care of surgical patients. Effective post-operative pain is an essential component of the care of the patient. Inadequate pain control, apart from being in human may result in increased morbidity and mortality.[1] Good analgesia can reduce deleterious effects. Afferent neural blockade with local anesthetics is the most effective analgesic technique. Next in order of effectiveness are high dose opioid therapy and NSAIDS.

Regional anesthesia avoids the complications of general anesthesia and also intubation while providing adequate analgesia and muscle relaxation in the operative area. It thus is a good alternative to general anesthesia. It also provides post-operative pain relief. Spinal anesthesia is a simple technique with rapid onset of action most commonly used in vaginal hysterectomy.[2] Most common Local anesthetic used for spinal anesthesia is bupivacaine, but due to short duration of action early analgesic intervention in the post-operative period is required.[3] A number of adjuvants to local anesthetics have been used intrathecally to prolong the intra-operative and post-operative analgesia. The addition of low doses of fentanyl and clonidine to local anesthetics during spinal anesthesia decreases the incidence of local anesthetic related side effects, reduces the time of onset of the sensory and motor blockade, and increases the quality of intra and post-operative analgesia by reducing the dose of local anesthetics.[4] Clonidine is a selective partial agonist for α_2-adrenoreceptor, with ratio of approximately 200:1 (α_2:α_1),[5] it has potent anti-nociceptive properties[6] and increases the duration of analgesia. Fentanyl is a synthetic opioid and μ receptor agonist, about 100 times more potent than morphine as an analgesic.[7] It is most commonly administered intravenously, although it is also commonly administered epidurally and intrathecally for acute post-operative and chronic pain management. Fentanyl not only improves the quality of intra-operative analgesia but also reduces the need of supplemental sedation.[8] In the present study, we tried to find out whether quality of anesthesia is better with low dose bupivacaine and clonidine or with low dose bupivcaine and fentanyl.

Aims and Objectives

Aim of our study was to evaluate the effectiveness of 0.5% bupivacaine with clonidine and 0.5% bupivacaine with fentanyl for spinal aneshthesia in terms of—

- Onset and duration of sensory blockade;
- Onset and duration of motor blockade;
- Duration of post-operative sedation;
- Duration of post-operative analgesia;
- Complications, if any.

Materials and Methods

Study Design

After obtaining institutional and ethical committee approval, written informed consent was taken from all patients prior to joining the study. Study was a prospective, randomised double-blind, controlled, single centre study. 80 patients ASA grade I and ASA grade II scheduled for vaginal hysterectomy were randomly allocated into two groups by using computer generated random numbers.

Inclusion Criteria

ASA Grade I and II patients posted for vaginal hysterectomy, aged between *45* and *65 years*, normotensive patients.

Exclusion Criteria

ASA Grade III and IV patients, patients with significant cardiovascular, renal, hepatic dysfunction, having contraindication for spinal anesthesia and morbidly obese patients.

Blinding

The drug solution to be used for spinal anesthesia was prepared by another anesthetist according to the randomization chart. The randomization code was sealed in an envelope. The code number of each individual was also sealed in the envelope.

Sample size

Sample size is calculated by using the pilot study of 25 patients with parameter duration of motor block

in minutes. Group BC = Mean ± SD is *198.6 ± 43.6 min* and Group BF = Mean ± SD is *174 ± 15.8 min*. By using formula:

$$\frac{2XZ\alpha + Z_{(1-\beta)})^2 \times (SD)^2 combined}{d^2}$$

$Z\alpha = 1.96$, $Z_{1-\beta} = 0.84$;

Combined SD = 38.39;

Difference of means (d) = 24.3;

Minimum required sample size (n) = 39.13≈40 per group. **Group BC (n = 40):** Patients received 0.5% Hyperbaric bupivacaine *2.8 ml* (*14 mg*) + *25 mcg* Clonidine; **Group BF (n = 40):** Patients received 0.5% hyperbaric bupivacaine *2.8 ml* (*14 mg*) + *30 mcg* Fentanyl.

Study plan

Pre-anesthetic evaluation was carried out in detail which included general examination, systemic examination, airway assessment, spine and neck examination. All baseline investigations were done including hemoglobin, platelet count, bleeding time, clotting time, blood sugar level, liver function tests, renal functions tests, serum electrolytes, ECG and chest *X*-ray PA view. Group BC (n = 40) received 0.5% Hyperbaric Bupivacaine *2.8 ml* (*14 mg*) + *25 mcg* Clonidine and group BF (n = 40) received 0.5% Hyperbaric Bupivacaine *2.8 ml* (*14 mg*) + *30 mcg* Fentanyl intrathecally. Pre-operatively pulse rate, blood pressure, oxygen saturation were noted. After shifting the patient on operating table monitors like ECG, NIBP, pulse oxymeter were attached. Intravenous canula of 18 G was secured and pre-loading done with *10 ml/kg* of Ringer lactate solution and pre-medicated with inj. Ondensetron *0.08 mg/kg* I.V. and inj. Ranitidine *1 mg/kg* I.V. before giving spinal anesthesia. Painting and draping done in sitting position under all aseptic conditions. After palpating L3-L4 space subarachanoid block was given in Group BC patients with 0.5% Hyperbaric Bupivacaine *2.8 ml* (*14 mg*) + *25 mcg* Clonidine and in Group BF patients with 0.5% Hyperbaric Bupivacaine *2.8 ml* (*14 mg*) + *30 mcg* Fentanyl with 25 G spinal needle. Supine position was given immediately. All patients were given supplemental oxygen by venti mask @4–6 lit/min.

Intra-operative monitoring

Intra-opratively pulse rate, blood pressure, O_2 saturation, ECG was monitored, Sensory block was assessed by a pin prick test performed with 22 G short bore needle. Motor block was assessed using by using Bromage score:

Bromage 0	Patient is able to move hip, knee and ankle
Bromage 1	Patient unable to move hip but able to move knee and ankle
Bromage 2	Patient unable to move hip and knee but able to move ankle
Bromage 3	Patient unable to move hip, knee and ankle

After intrathecal drug injection, intra-operatively data was recorded during 1st *2 hours* at *5,15, 30, 45, 60,90,120 minutes*. During surgery, patient did not receive any sedation.

Post-operative monitoring

Assesment of post-operative sedation done by using Ramsay sedation scale.

Score	Level of sedation
1	Anxious or agitated or restless or both
2	Co-opreative, oriented and tranquil
3	Responding to commands only
4	Brisk response to light glabellar tap
5	Sluggish response to light glabellar tap
6	No response to light glabellar tap

Assesment of post-operative analgesia done by using Visual Analogue Scale between 0 and 10. 0-No pain: 10-most severe pain**.** Post-opearatively data was recorded for first *4 hour* every hourly, for next *8 hours* every *2 hourly*, for next *12 hours* every *6 hourly* interval upto *24 hours*. Duration of Anesthesia was measured as time interval from intrathecal injection to regression of sensory block below L1.

Monitoring and treatment of side effects

Intra-operative and post-operative side effects such as nausea, vomiting, hypotension, bradycardia, shivering and sedation were noted till complete recovery. Hypotension was defined as a decrease in systolic blood pressure more than 30% of baseline value. Hypotension was treated with oxygen supplementation, I.V. fluids or Mephenterine. Bradycardia (Pulse rate < 60) treated with inj. Atropine. Inj Ondensetron *0.08 mg/kg* used for nausea and vomiting. Inj. Naloxone was kept ready for respiratory depression.

Statistical analysis

Statistical evaluation was done by using 2 independent sample *t*-test and Mann-Whitney *U*-test. The detailed data was entered into well tabulated Microsoft Excel sheet and subsequently

analyzed statistically. Graphical display was done for visual inspection, *p* - value less than 0.05 was considered to be significant.

Results

There was no statistical difference among groups as far as age, weight, height, and duration of surgery concerned. Mean duration of onset to peak sensory block (*5.45 ± 0.50 min*), onset to peak motor block (*7.05 ± 0.22 min*) was significantly higher in Group BC as compared to Group BF (*6.90 ± 0.38 min*) and (*8.67 ± 0.47 min*) respectively. Significant difference in mean duration of sensory block and motor block (*189.80 ± 6.49 min*, *247.28 ± 8.42 min*) in Group BC and Group BF (*150.23 ± 4.23, 197.08 ± 6.25 min*) were noted. Duration of post-operative analgesia was significantly higher in group BC (*495.93 ± 22.43 min*) as compared to group BF (*269.33 ± 17.98 min*). There was significant difference between VAS score in group BC and group BF except 4^{th} *hr* and 18^{th} *hr*. All patients were hemodynamically stable and no significant difference in post-operative sedation and adverse effects was observed, (**Tables 1–4** are showed & **Figs. 1–3** are displayed).

Table 1: Onset to peak sensory and complete motor block duration

	Group BC (n = 40)		Group BF (n = 40)		p - value
	Mean	SD	Mean	SD	
Onset to peak sensory block	5.45	0.50	6.90	0.38	< 0.001
Onset to motor block (Grade IV)	7.05	0.22	8.68	0.47	< 0.001

*Significant

By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean onset of sensory block and onset of motor block in Group BC and Group BF.

Table 2: Mean duration of sensory and motor block

	Group BC (n = 40)		Group BF (n = 40)		*p* - value
	Mean	SD	Mean	SD	
Duration of sensory block	189.80	6.49	150.23	4.23	< 0.001*
Duration of motor block	247.28	8.42	197.08	6.25	< 0.001*

*Significant

By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean duration of sensory block and motor block in Group BC and Group BF.

Table 3: Mean duration of analgesia

Group	Number of patients	Duration of Analgesia (min)		*p* - value
		Mean	SD	
Group BC	40	495.93	22.43	< 0.001*
Group BF	40	269.33	17.98	

*Significant

By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean duration of analgesia (*min*) in Group BC and Group BF.

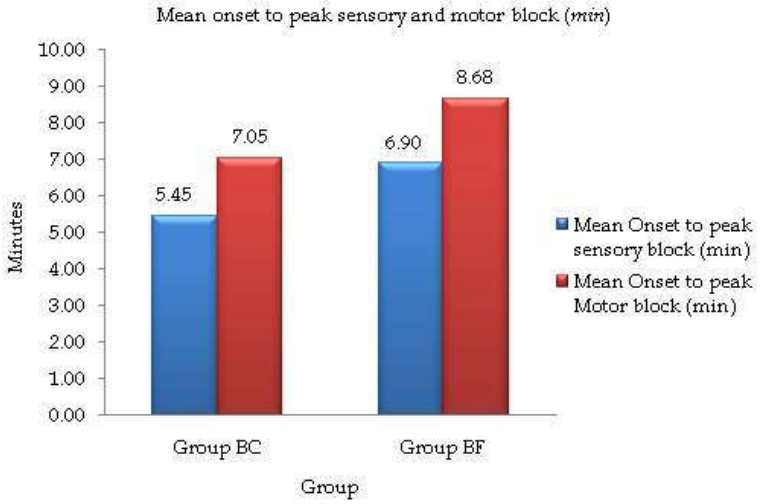

Fig. 1: Onset to peak sensory and complete motor block duration

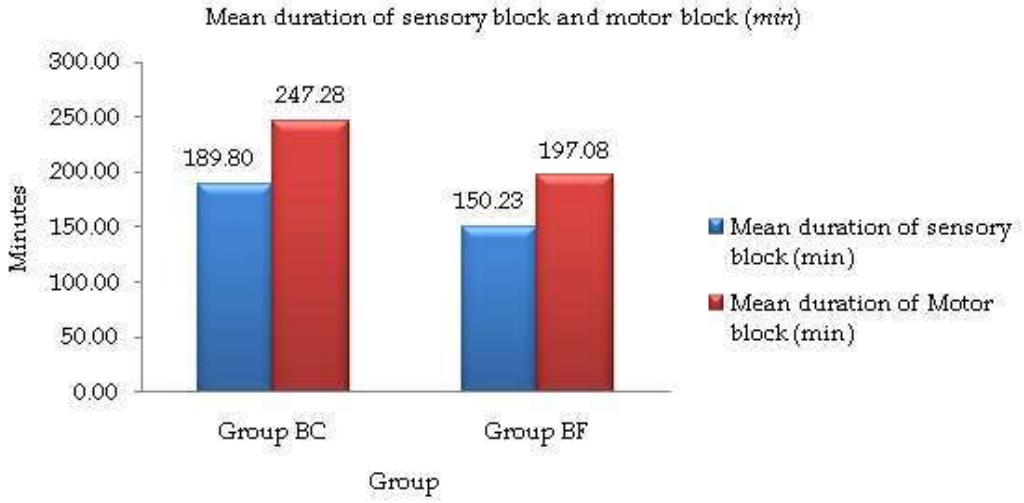

Fig. 2: Mean duration of sensory and motor block

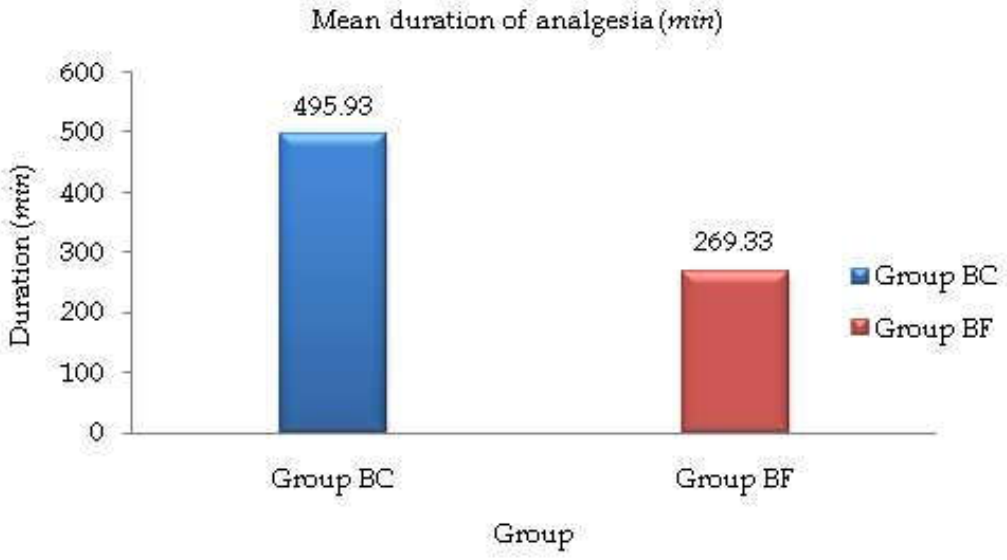

Fig. 3: Mean duration of analgesia

Table 4: Mean visual analogue scale

VAS at	VAS						*p* - value
	Group BC			Group BF			
	Min.	Max.	Median	Min.	Max.	Median	
1 hr	0	0	0	0	2	0	0.043*
2 hr	0	0	0	1	5	2	< 0.001*
3 hr	0	0	0	0	6	5	< 0.001*
4 hr	0	0	0	0	5	0	0.079
6 hr	1	5	2	0	3	1	< 0.001*
8 hr	0	6	5	2	6	3	< 0.001*
10 hr	1	2	1	0	6	5	< 0.001*
12 hr	2	5	2	0	4	0	< 0.001*
18 hr	2	6	5	5	6	5	0.876
24 hr	2	6	2	2	5	3	< 0.001*

*Significant

By using Mann-Whitney *U*-test p - value < 0.05 therefore there is significant difference between VAS score in Group BC and Group BFexcept 4^{th} *hr* and 18^{th} *hr*.

Discussion

Local anesthetics are commonest agents used for spinal anesthesia, but due to their relatively short duration of action, post-operative period needs the early analgesic intervention.[9] Clonidine is selective partial agonist for α_2 adrenoreceptors.[10] The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic α_2 receptors in substantia gelatinosa of spinal cord. It works by blocking the conduction of C and Aδ fibers.[11] It also increases potassium conductance in isolated neurons *in vitro* and intensifies conduction block of local anesthetics. Fentanyl is a potent synthetic opioid analgesic with rapid onset of action.[12] It binds to μ-opioid G-protein coupled receptor, which inhibit pain neurotransmitter release by decreasing intra-cellular calcium levels.

Addition of fentanyl or clonidine to bupivacaine may help in increasing the duration of sensory and motor blockade, post-operative analgesia and decrease the dose of local anesthetic.In this present study there was no statistical difference among groups in age, height, weight and duration of surgery.

In our study, we observed the significant difference between mean Systolic Blood Pressure (SBP) in Group BC and Group BF at *15 min to 45 min*. (p < 0.05) and significant difference between mean Diastolic Blood Pressure (DBP) in Group BC and Group BF at *15 min*, *30 min* and *at 60 min* (p < 0.05). Our results were comparable with study conducted by Agarwal D *et al.*[13] for SBP. There is no significant difference between mean pulse rate in Group BC and Group BF at pre-operative to *120 min*, (p > 0.05).

We found that the duration of sensory blockade was *189.80 ± 6.49 min* and the duration of motor blockade was *247.28 ± 8.42 min* in patient receiving clonidine with bupivacaine. Sethi BS[11] *et al.* has also shown the comparable results in which the duration of sensory blockade was *218 min* (*150–240 min*) and duration of motor blockade was 205 (*90–300 min*) in patient receiving clonidine (*1 mcg/kg*) with bupivacaine.

Similarly the duration of analgesia was *495.93 ± 22.43 min* in patients receiving clonidine with bupivacaine. Shah BB[4] *et al.* found the similar results where the duration of analgesia in clonidine (*30 mcg*) Group was *436.65 ± 149.84 min*.

In our study, we observed that the time to reach peak sensory level was *6.90 ± 0.38 min*, duration of sensory block was *150.23 ± 4.23 min* and the duration post-operative analgesia was *269.33 ± 17.98 min* in Group BF. Our findings were similar to the study conducted by Dhumal PR[14] *et al.* where the time to reach peak sensory level was *5.03 ± 1.45 min*, duration of sensory block was *121.3 ± 11.4 min* and the duration of post-operative analgesia was *225.3 ± 29.2 min* in patients receiving fentanyl (*25 mcg*) with bupivacaine. Another study conducted by Gauchan S[15] *et al.* has also revealed the comparable result for peak sensory level where the time to achieve peak sensory level was *6 ± 2.5 min* with *20 mcg* fentanyl.

The time to reach peak sensory level was *5.45 ± 0.50 min* and the duration of motor block was *197.07 ± 6.24 min* in Group BF. Our results were comparable with the study conducted by Sanchan P[16] *et al.* in which they found that the time to reach peak sensory blockade was *4.43 ± 0.26 min* and the duration of motor block was *189.50 ± 16.31 min* with *75 mcg* of clonidine.

Besides, the duration of sensory block was *189.80 ± 6.49 min* and time for first analgesic request was *495.93 ± 22.43 min* in Group BC. Khezri MB[12] *et al.* found similar results where the mean duration of sensory block was *169.66 ± 25.69 min* and time for first rescue analgesic was 519*.44 ± 86.25 min* in patients receiving clonidine (*75 mcg*) with bupivacaine.

In our study, the mean duration of motor block was *247.28 ± 8.42 min* and the duration of post-operative analgesia was *495.93 ± 22.43 min* in Group BC. Singh RB[17] *et al.* found that the mean duration of motor block was *280.80 ± 66.88 min* and the duration of post-operative analgesia was *510.6 ± 133.64 min* in patients receiving clonidine (*50 mcg*) with bupivacaine.

The duration of sensory block was *189.8 ± 6.49 min* and 150.22 ± 4.22 min and the duration of motor block was *247.27 ± 8.42 min, 197.07 ± 6.24 min* in BC and BF Group respectively. Number of diclofenac injections used in BC Group was 2 & 3 (median 2) and it was 3 & 4 (median 3) in BF Group. Chopra P[5] *et al.* found the comparable results where the duration of sensory block was *177.8 ± 43.8 min* and it was *142.2 ± 14.7 min* in patients receiving clonidine (*30 mcg*) and fentanyl (*15 mcg*) respectively. The duration of motor block in clonidine Group was *206.6 ± 43.6 min* and it was *166.2 ± 15.8 min* in fentanyl Group. Number of diclofenac injections used in clonidine Group was 1.16(1 & 2) and it was 2.66G (2 & 3) in fentanyl group.

We found that the mean time to reach peak sensory level was *5.45 ± 0.50 min* in Group BC and it was *7.05 ± 0.22 min* in Group BF. Bhattacharjee A[7] *et al*. found that the mean time to reach peak sensory level in clonidine (*75 mcg*) Group was *6.25 ± 2.13 min* and it was *6.46 ± 3.29 min* fentanyl (*25 mcg*) group.

Besides, the time to reach peak sensory level was *6.902 ± 0.38 min*, time of regression of motor block to Bromage scale 0 was *197.07 ± 6.24 min* and mean duration of analgesia was *269.32 ± 17.98 min* in Group BF. Bacha UQ[18] *et al*. has also shown the similar results in which the time to reach peak sensory level was *7.4 ± 0.756 min* and time of regression of motor block to Bromage scale 0 was *188.1 ± 6.22 min* and mean duration of analgesia was *256.1 ± 21.328 min* with *2.5 ml* bupivacaine + *25 mcg* of fentanyl.

In Our study, the mean duration of sensory block was *189.8 ± 6.49 min* and mean sedation score was 2 in Group BC. We observed hypotension in 1 patient and bradycardia in 2 patients. Baj B[9] *et al.* found similar results where the mean duration of sensory block was *192.50 ± 31.39 min* and mean sedation score by using Ramsay sedation score was *2.03 ± 0.414 min* with *25 mcg* of clonidine. They also noted hypotension in 2 patients and bradycardia in 3 patients.

Conclusion

To conclude, *30 mcg* clonidine and *25 mcg* fentanyl is an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures of prolonged duration with minimal side effects and excellent quality of spinal analgesia. Clonidine when compared with Fentanyl, offers a better effect owing to earlier onset and prolonged duration of sensory and motor blockade as well as longer duration of post-operative analges.

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Role of Perfusion Index as a Tool for Acute Post-operative Pain Assessment: An Observational Study

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Abstract

Background: A painful stimulus can produce vasoconstriction and a decrease in perfusion index (PI). The visual analog scale (VAS) is the most common pain assessment scale. However, it is affected by psychometric instability. This study was designed to evaluate the correlation between VAS as a subjective indicator of pain and PI as an objective indicator of pain. *Materials and Methods:* At the post-anesthesia care unit, the perfusion index was checked to 50 adult patients of ASA-I who underwent laparoscopic surgery. At the time of the first request for analgesia (T1) VAS was recorded together with the PI, heart rate (HR), Mean Arterial Blood Pressure (MAP), peripheral oxygen saturation and following which analgesia was given. Thirty minutes thereafter, (T2) second measurements for the mentioned parameters were taken. *Results:* The PI was significantly higher at T2 than at T1 (mean increase % = 90% vs 81.4%). This increase was associated with a statistically significant decrease in VAS, HR, and MAP. This means that the PI increases with adequate relief from pain, as indicated by a decrease in VAS, HR, and MAP. A decrease in VAS was associated with an increase in PI, but the correlation was not statistically significant as the degree of the increase in PI in relation to the decrease in VAS was variable among patients. *Conclusion:* PI can be added to other indicators of pain assessment in the post-anesthesia care unit.

Keywords: Pain; Perfusion index; Post-anesthesia care unit; Visual analog pain score.

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Introduction

Un-relieved post-operative pain can result in serious side effects that affect the respiratory system (atelectasis, retention of secretions, pneumonia), the cardiovascular system (hypertension, arrhythmias, coronary ischemia), the gastrointestinal system (decreased bowel movement, nausea, vomiting) and the endocrinal system (increased catecholamine secretion). It also promotes thromboembolism by delaying mobilization.[1]

The International Association for the Study of Pain (IASP) defines pain as 'An unpleasant sensory and emotional experience associated with actual or

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potential tissue damage, or described in terms of such damage'.[2] Effective pain management requires careful assessment and continuous review of pain. The objectives of pain assessment are to measure the severity of pain, select the appropriate analgesic, and estimate the response to treatment. Pain is a subjective symptom as the individual can describe his own feelings. Thus, emotional and psychological factors may interfere with the assessment of the physical component of pain. Self-report pain scales have been the most common pain assessment tools over the years. The visual analogue scale (VAS) is the most common pain assessment scale.[3–5] Both VAS and numeric rating scale have been proven to be superior to a four-point verbal categorical rating scale.[6] However, their validity cannot be established in every environment because of the difference in psychometric stability.[7]

The pulse oximetry system can measure the perfusion index (PI) at the monitored site by calculating the relation between pulsatile and static blood in peripheral tissues. The PI is an indirect, non-invasive, and continuous measure of peripheral perfusion. It ranges from 0.02% (very weak pulse strength) to 20% (very strong pulse strength). It can also measure PI in conjunction with oxygen saturation and pulse rate by simple application of the pulse Oximeter probe to the finger. By knowing, the highest recorded PI, the best monitoring site for pulse oximetry can be identified. The changes in sympathetic nervous tone affect smooth muscle tone and can alter the level of perfusion.

Temperature, volume, and anesthetics can affect the perfusion at the extremities by causing vasoconstriction and vasodilatation, which can cause a decrease in PI or an increase in PI, respectively. The measurement of PI is not affected by Heart Rate (HR) variability, SpO_2, or oxygen consumption.[8,9]

Most anesthetics produce a vasodilator effect while pain induces vasoconstriction. A study had investigated whether a painful stimulus can produce vasoconstriction and a decrease in PI in normothermic anesthetized patients.[8] The researchers found that the PI decreased during painful stimuli in anesthetized volunteers at different concentrations of sevoflurane. They hypothesized that an increased PI after anesthetic administration can be an early indicator of successful anesthesia, whereas absence of this increase may be an early warning of anesthetic failure. Hence, it could be a valuable tool for pain assessment under anesthesia.

Laparoscopic surgery is associated with severe acute post-operative pain unless it is well managed. As far as we know, no study has investigated the correlation between VAS as a subjective indicator of pain and PI as an objective indicator of pain. This correlation can be of great help in analgesic guidance in Post-anesthesia Care Unit (PACU) and unconscious patients in ICUs.

Aim of Work

The aim of the study was to correlate pulse co-oximetry PI with VAS and evaluate the possibility of its use as an objective tool for post-operative pain assessment.

Materials and Methods

A prospective, observational study was performed in Indira Gandhi Institute of Medical sciences, Patna after obtaining the approval of the Ethical Committee and informed written consent from patients undergoing elective Laparoscopic surgery.

Inclusion Criteria

Patients of ASA-I, aged *18–50 years*, who were conscious enough to co-operate and whose mental status was normal in the immediate post-operative period were enrolled in the study.

Exclusion Criteria

Patients with pre-existing cardiovascular, pulmonary or metabolic diseases or history of a neurological, psychiatric or chronic pain disorder, who were taking psychotropic drugs, patients with allergy to any drug used in the study, those with unstable hemodynamic status, and unconscious were excluded.

Pre-operatively, patients were trained on how to express their pain level using VAS to increase their familiarity with the scale. VAS is a subjective tool that depends on the patient's self-expression. The scale consists of a *10 cm* horizontal line. Patients can make a mark on the line according to their pain intensity that can range from *0 to 10*.

The patients were premedicated with intravenous (I.V.) *1 mg* midazolam, *40 mg* pantoprazole, *75 μg* palonosetron and *8 mg* dexamethasone. In the operating room, standard monitors were applied like ECG, pulse oximeter and non-invasive arterial blood pressure monitor. Pre-oxygenation was carried out for *3 min* by means of a face mask with 100% oxygen. Anesthesia was induced by I.V. fentanyl *2 μg/kg*, propofol *2.5 mg/kg* and atracurium

0.5 mg/kg. After endotracheal intubation, capnography and a temperature nasopharyngeal probe were applied. The lungs were ventilated with a tidal volume of *6–8 ml/kg* and the ventilatory rate was adjusted to maintain $EtCO_2$ between *35* and *40 mm Hg*. Maintenance was done with 1.5 MAC isoflurane and top-up doses of atracurium. Analgesia was maintained with I.V. fentanyl at *0.5 μg/kg/h*. The intra-operative Mean Arterial Blood Pressure (MAP) was kept around *60 mm Hg*. Patients who required I.V. nitroglycerine or ephedrine were excluded from the study. Warm I.V. Ringer's acetate solution was infused to replace fluid deficit and basal fluid requirements. The patient was kept warm by maintaining the room temperature at 25°C. At the end of the operation the muscle relaxant was reversed and all patients trachea were extubated and sent to the PACU.

At the post-anesthesia care unit

The following monitors were attached to the patient: ECG, non-invasive arterial blood pressure monitor and finger tip Pulse Oximeter (Romsons's Oxee Check). The Oximeter probe used to monitor the PI was attached to the middle fingertip of the hand contralateral to the site of blood pressure monitoring and was wrapped in a towel to decrease heat loss and interference by ambient light. An oxygen mask was applied if SpO_2 was below 90%. The patients were kept warm with wool blankets, warm I.V. fluids, and a warm air-forced device.

Observation

All patients were observed until they asked for analgesia like at the time of the first request for analgesia (T1) VAS for pain intensity was recorded, together with the PI. Simultaneously, HR, MAP and peripheral oxygen saturation were also noted. For all patients analgesia was achieved with I.V. morphine at *0.05 mg/kg* and I.V. *1 g* paracetamol vial.

Thirty minutes after post-operative analgesia (T2), second measurements of the above-mentioned parameters were taken simultaneously like VAS for pain intensity, PI, HR, MAP, peripheral oxygen saturation, and axillary temperature.

Statistical analysis

Data were statistically described in terms of mean ± SD. Comparison of the time point values was done using the paired *t*-test. *P* - values less than 0.05 were considered statistically significant. All statistical calculations were performed using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) release 15 for Microsoft Windows (2006).

Power analysis

Power analysis was carried out by comparing all variables between the two study time points. The paired *t*-test was chosen to perform the analysis. α-Error level was fixed at 0.05 and the sample size at 50 participants. The statistical power of our comparisons is shown in the (**Table 1)** below. Calculations were performed using PS Power and Sample Size Calculations Software, version 3.0.11, for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Results

The study initially comprised 62 patients who underwent laparoscopic surgery. All patients who met the inclusion criteria were enrolled in the study. Twelve patients were excluded as they required I.V. nitroglycerine or ephedrine intra-operatively. Finally, 50 patients completed the study. The demographic characteristics of the patients were as follows: Sex, 24 women and 26 men; age, *34.24 ± 12.53 years*; and BMI, *24.76 ± 4.27 kg/m²*. There was a statistically significant increase in PI at T2 than at T1. The mean increase % equalled 90.0 ± 81.4% (**Table 1**).

Table 1: The perfusion index, visual analog scale, mean arterial pressure, and heart rate at T1 and T2, their difference between T2 and T1.

***N* = 50**	**Perfusion Index (PI)**	**Visual Analogue Scale (VAS)**	**MAP (*mm Hg*)**	**HR (*beats/min*)**
T1 (at first request of analgesia)	1.08 ± 1.04	6.75 ± 1.34	84.58 ± 11.24	81.68 ± 13.76
T2 (*30 min* after analgesia)	1.76 ± 1.71	1.86 ± 1.24	81.48 ± 10.14	78.49 ± 12.64
Difference between T2 and T1	0.81 ± 0.94	-4.63 ± 1.44**	-3.4 ± 3.64**	-11.08 ± 5.94**

Values were presented by mean ± SD, *N = Number of patients*.

***Highly Significance** ($p < 0.001$).*

Discussion

Pain is a subjective and personal experience that makes objective measurements impossible.[6] However, the increase in sympathetic nervous tone caused by pain can affect the PI, which can be a guide for the given analgesics in PACU. This tool for pain assessment can eliminate the variations in personality, age, sex, and cultural background. It can also eliminate psychological factors such as fear, anxiety, depression, and anger.

In this study, the PI was significantly higher at T2 than at T1 (mean increase % = 94.3 ± 82.7%). This increase was associated with a statistically significant decrease in VAS, HR, and MAP. The mean decrease % was 70.5 ± 19.88%, 11.1 ± 7.2%, and 3.96 ± 5.01% in VAS, HR, and MAP, respectively. This means that the PI increases with adequate relief from pain as indicated by a decrease in VAS, HR, and MAP. A decrease in VAS was associated with an increase in PI but the correlation was not statistically significant as the degree of the increase in PI in relation to the decrease in VAS was variable among patients.

This study was similar to a study conducted by Hagar *et al.* in which an electrical current was applied to the anterior thigh in two healthy volunteers anesthetized with propofol and maintained with sevoflurane at different concentrations (1, 1.5, 2, 2.5%).[8] This painful stimulus produced a significant increase in HR and MAP with a significant decrease in PI. They concluded that the PI may be of clinical value in assessing pain in the anesthetized state.

A new-generation finger tip pulse oximeter (Romsons's Oxee Check) is easily available and the easiest of all peripheral perfusion assessment modalities. It enables physicians to obtain reliable measurements even under difficult clinical conditions: Patient's movements, hypotension, hypothermia, or electromagnetic field of other devices because of the presence of reference signal calculations, the adaptive filter, and transformation of a single saturation signal.

Pain can alter the endocrine system leading to increased catecholamine secretion causing vasoconstriction.[1] It was reflected as decreased PI with high VAS, but after receiving analgesia the PI increased significantly.

PI was used before for prediction of the onset of successful regional sympathetic blocks, by measuring PI before and after block, like the onset of the epidural anesthesia, which was associated with an increase in PI [10–11]

Conclusion

Perfusion index can be added to other indicators of pain assessment in PACU. It is easy, non invasive, free of subjective interpretation and low time consuming.

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Original Research Article

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Comparison between Ropivacaine and Ropivacaine Plus Tramodol in Wound Infiltration as an Analgesic after Open Cholecystectomy Surgeries for Post-operative Analgesia

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Abstract

Post-operative pain is common after abdominal surgery and is a major cause of patient dissatisfaction in post-operative period. Various drugs like opioids, nonsteroidal anti-inflammatory drugs, dexamethasone has been used to control post-operative pain but efficacy is variable. Wound infiltration is being used now-a-days to provide analgesia in immediate post-operative period. Ropivacaine, a newer longer acting local anesthetic, is used due to its less side effects. Tramadol can be used to as an adjuvant to ropivacaine in wound infiltration. A total of 75 patients, posted for open cholecystectomy, were randomly divided into three groups. Group C – inj. normal saline *22 ml*, Group R- 0.375% ropivacaine *20 ml* + inj. normal saline *2 ml*. Group RT- 0.375% ropivacaine *20 ml* + inj. tramadol *2 mg/kg* in *2 ml*. A total volume of *22 ml* was infiltrated. Local wound infiltration was done at time of closure according to study groups.VAS score in post-operative period, time for first rescue analgesic, number of rescue doses in first *24 hrs*, PONV and patient satisfaction were noted. There was higher VAS score and early requirement of rescue dose in control group compared to group R and RT ($p < 0.001$). There was also longer duration of analgesia in group RT compared to group R ($p < 0.05$). Incidences of PONV were comparable in all three groups. Ropivacaine and ropivacaine-tramodol were effective in wound infiltration for post-operative analgesia but later was preferred due to longer duration of action and better patient satisfaction without increased incidence of PONV.

Keywords: Infiltration; Ropivacaine; Tramadol.

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Introduction

Post-operative pain is inevitable after major upper abdominal surgeries like open cholecystectomy. Post-operative pain may cause stress response to body and respiratory or cardiac complications.[1–3] So, post-operative pain should be controlled as early as possible.

Post-operative analgesia is important part of optimal peri-operative management. Currently various methods are available for post-operative pain control like epidural analgesia, intravenous analgesia and patient controlled analgesia pump.[4] Opioids are mainstay of post-operative pain control but are associated with some adverse side effects like respiratory depression, sedation, nausea

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and vomiting.[5–7] Nonsteroidal anti-inflammatory drugs are less effective as sole analgesic after upper abdominal surgeries. Local anesthetic methods are more useful than intravenous analgesia with less side effects irrespective of surgical procedure.[8]

Now-a-days, wound infiltration with local anesthetic drugs is widely used in various surgeries as a part of optimal post-operative pain control.[9,10] Wound infiltration is safe, effective and inexpensive method of post-operative pain control. It provides immediate analgesia lasting for few hours without major side effects.[11,12]

Bupivacaine and ropivacaine are commonly used local anesthetics in wound infiltration due to longer duration of action.[13] Ropivacine has wider safety profile and associated with less adverse events. 0.375% and 0.5% concentrations of ropivacaine are commonly used for wound infiltration for post-operative analgesia.[14,15] Various adjuvants are used in addition to local anesthetics to potentiate effects of local anesthetics and reduce rescue analgesic requirement.[5,16,17]

Tramadol is commonly used in wound infiltration due to its safety and efficacy. Tramadol is weak opioid and its local anesthetic effects have been demonstrated in various studies.[18] As an adjuvant in wound infiltration, tramadol can potentiate effects of local anesthetics without systemic side effects.[13] Tramadol has less potential for respiratory depression and abuse unlike other commonly used opioids.[19]

Aims

Aim of our study was to compare effectiveness of wound infiltration with ropivacaine alone and ropivacaine plus tramodol after open cholecystectomy surgeries in term of post-operative analgesia. Secondary outcomes measured were time for first rescue analgesic, number of rescue doses in first *24 hrs*, patient satisfaction and side effects if any.

Materials and Methods

This prospective randomized double blind study was carried out in our institute from Nov 2018 to March 2019. A total of 75 patients of age group *20–50 years*, either gender, belonging to ASA I/II posted for elective open cholecystectomy surgeries were selected in our study. Written informed consent was taken from each patient. Patients were divided into three groups, 25 patients in each group.

Exclusion Criteria

- Patient refusal
- Allergy to local anesthetic drugs
- Liver dysfunction
- Renal dysfunction
- History of treatment on pain medications or opioids use
- Severe un-controlled comorbities like diabetes, hypertension
- Bleeding disorders

Meticulous pre-operative evaluation was carried out on day before surgery. Visual Analogue Score (VAS) was used to grade intensity of pain in post-operative period. Patients were given information about VAS score grading pre-operatively. VAS is pain measurement tool ranging from 0 to 10, 0-no pain, 10-most severe pain. All patients were premedicated with inj. gycopyrrolate *4 mcg/kg* and inj. midazolam *1 mg* intravenous *30 minutes* before surgery. All patients were induced with general anesthesia. All patients of three groups were induced with inj. sodium pentothal *6 mg/kg* and inj. succinylcholine *1.5 mg/kg*. All patients were given inj. fentanyl *1.5 mcg/kg*. Anesthesia was maintained with oxygen, sevofluarne 1 MAC and inj. atracurium. At time of wound closure, muscle, subcutaneous tissue and skin infiltration were carried out by operating surgeon with total volume of *22 ml* according to study group. Randomization was done with sealed envelope technique.

Group C – Inj. Normal saline (0.9%) - Total volume *22 ml*;

Group R – Inj. Ropivacaine (0.375%) *20 ml* + Inj. Normal saline *2 ml* - Total volume *22 ml*;

Group RT – Inj. Ropivacaine (0.375%) *20 ml* + Inj. Tramadol (*2 mg/kg*) in *2 ml*-Total volume *22 ml*.

At the end of surgery, patients were reversed from neuromuscular blockade with inj. glycopyrrolate *8 mcg/kg* and inj. neostigmine *0.05 mg/kg*. Hemodynamic parameters were recorded intra-operatively and immediate post-operative period upto *24 hrs*. Post-operative pain was measured using VAS score in immediate post-operative period, *30 min*, *1 hr*, *2 hr*, *4 hr*, *6 hr*, *8 hr*, *12 hr*, *18 hr* and *24 hr*. VAS score > 3 at anytime was noted and rescue drug in form of inj. diclofenac *1.5 mg/kg* I.V. slowly was given. VAS score at different time interval and time for first rescue analgesic were recorded. Number of rescue doses in first *24 hrs* in post-operative period and incidences of post-operative nausea/vomiting were also recorded.

Patient satisfaction score at 24 hr was also recorded using patient satisfaction scale (0–4), 0-poor to 4-excellent. Operating surgeons whose had done infiltration and anesthesiologists taking follow up in post-operative period were kept blind to study drug administered.

Statistical Analysis

All data were collected and analysed with SPSS 17 software. Statistical methods such as Anova test, student's *t*-test and chi-square test were performed to find level of significance of our data values for all three groups. Level of significance was set to $p < 0.05$.

Results

All 75 patients of three groups were assessed and results were shown in (**Tables 1–5**).

Table 1: Demographic characteristics

	Group C	Group R	Group RT	*p* value
Age	34.56 ± 12.35	33.38 ± 10.79	36.78 ± 12.88	> 0.05
Sex (M/F)	20:5	18:7	21:4	> 0.05
ASA I/II	24/1	23/2	24/1	> 0.05
Weight	62.10 ± 11.67	66.45 ± 13.01	63.78 ± 15.89	> 0.05
Duration of surgery	81.78 ± 16.68	85.98 ± 13.85	84.87 ± 14.37	> 0.05

All patients of three groups were comparable in demographic profiles, ASA status and duration of surgery ($p > 0.05$) (Table 1).

There was no difference in VAS score till post-operative period *1 hr* for all three groups. There was significant increase in VAS score around *1 hr* in Group C, difference is statistically significant ($p < 0.05$). VAS score were comparable in Group R and Group RT during all times except *4 hr*, *6 hr* and *8 hr*, ($p > 0.05$) (Table 2).

Time for first rescue analgesic was significant shorter in Group C compared to other two groups ($p < 0.05$). There was also significant difference in time for first rescue analgesic for Group R and Group RT, shorter in group R ($p < 0.05$). Number of rescue doses requirement in first *24 hrs* was highest for Group C and least for Group RT, difference is statistically significant, ($p < 0.05$) (Table 3).

Table 4: PONV incidence

	Group C	Group R	Group RT	*P* value
Nausea/vomiting (First *24 hrs*)	5 (20%)	4 (16%)	5 (20%)	> 0.05

There was no significant difference in incidences of PONV in first *24 hrs* for all three groups ($p > 0.05$) (Table 4).

Table 5: Patient satisfaction scale

	Group C	Group R	Group RT	*p* value
Patient satisfaction scale (At *24 hrs*)	1.56 ± 0.56	2.05 ± 0.57	2.89 ± 0.67	< 0.05

Patient satisfaction at *24 hrs* was higher with group R and RT compared to Group C. There was significant difference for level of patient satisfaction for Group R and RT, higher satisfaction with Group RT ($p < 0.05$) (Table 5).

Table 2: VAS score in post-operative period

	0 *min*	30 *min*	1 *Hr*	2 *Hr*	4 *Hr*	6 *Hr*	8 *Hr*	12 *Hr*	18 *Hr*	24 *Hr*
Group C	2.06 ± 0.34	2.17 ± 0.34	2.67 ± 0.98	2.00 ± 0.37	2.10 ± 0.43	2.64 ± 0.83	2.20 ± 0.54	2.35 ± 0.46	2.43 ± 0.77	2.39 ± 0.33
Group R	1.78 ± 0.34	2.10 ± 0.67	2.14 ± 0.56	2.30 ± 0.45	2.89 ± 1.23	2.11 ± 0.87	2.08 ± 0.65	2.34 ± 0.54	2.53 ± 0.56	2.26 ± 0.34
Group RT	1.89 ± 0.56	2.30 ± 0.45	2.27 ± 0.56	2.10 ± 0.66	2.76 ± 0.97	2.23 ± 0.65	2.63 ± 0.64	2.23 ± 0.54	2.50 ± 0.87	2.13 ± 0.31

Table 3: Post-operative rescue dose requirement

	Group C	Group R	Group RT	*p* value
Time for first rescue dose	56.23 ± 16.67	280.78 ± 40.67	400.65 ± 50.34	< 0.001(C & R) < 0.001(C& RT) < 0.01 (R & RT)
Number of rescue doses in *24 hrs*	2.45 ± 0.78	1.46 ± 0.75	1.03 ± 0.65	< 0.001(C & R) < 0.001(C& RT) < 0.03 (R & RT)

Discussion

Pain is a protective body mechanism to injurious stimulus with or without actual tissue damage.[20] Individual variations in response to pain may be influenced by age, gender, genetic makeup and site of surgery.[21,22] Approximately 80–90% surgical patients experience moderate to severe pain post-operatively.[23,24] Post-operative pain due to surgical incision is nociceptive acute pain which is major cause of post-operative morbidity.

In-adequate control of post-operative pain has certain adverse health impacts on cardiovascular and respiratory system, like hypertension, tachycardia, in-adequate coughing, basal atelectasis, deep vein thrombosis, insomnia. Besides this, it delays early ambulation and prolong hospital stay.[25,26] Post-operative pain may be major cause of patient dissatisfaction after surgery. So, efforts should be always towards early and effective control of post-operative pain.

Management of post-operative pain is challenging after abdominal surgeries. Effective post-operative pain control can provide faster recovery, early hospital discharge and better patient satisfaction.[27]

Appropiate methods should be applied as early as possible to control pain in immediate post-operative period. Various drugs like, opioids and nonopioids drugs has been used to effectively control post-operative pain. Opioids are cornerstone for post-operative pain control. Morphine, fentanyl, sufentanyl are effective for moderate to severe post-operative pain. These drugs are associated with some side effects like respiratory depression, pruritus, urinary retention, nausea and vomiting which may cause patient discomfort.[5–7,28]

Nonsteroidal anti-inflammatory drugs like paracetamol, diclofenac, ketorolac are commonly used as second line drugs for post-operative pain control. These drugs are in-effective as sole analgesic after abdominal surgeries. As these drugs are less effective for moderate to severe pain which is common in immediate post-operative period.[8,28] They can be used as part of multimodal approach.

However, post-operative pain control is still demanding in first *24 hrs*. No single available method is effective for optimal post-operative pain control. Post-operative pain should be controlled effectively at earliest by multimodal approach so side effects of individual drugs could be minimized.[5] American society of anesthesiologists also stated that acute pain might be better controlled with multimodal analgesia.[29]

Wound infiltration is important part of a multimodal approach for post-operative analgesia. Local wound infiltration is attractive method as it is simple, effective and side effects are minimal.[3,30] Various studies have shown that incisional infiltration of local anesthetics was safe and effective technique for post-operative pain relief in orthopedic surgeries, abdominal surgeries and cesarean sections.[18,31–35] So we had chosen local anesthetics wound infiltration method for post-operative analgesia in open cholecystectomy surgeries.

Various local anesthetics, like bupivacaine and ropivacaine, are used in wound infiltration in various surgeries like open cholecystectomy. Local anesthetics used in wound infiltration block afferent pain signals from incision site and reduce sensitization of spinal dorsal horn neurons.[36,37] Local anesthetics can inhibit sensitization of nociceptive receptors that can cause in-flammatory response. Various studies have shown that infiltration with local anesthetics may reduce interleukin levels and increase substance *P* in the wound.[19]

Ropivacaine, longer acting anesthetic, has been widely used in local wound infiltration besides its use peripheral nerve blocks and epidural anesthesia. Ropivacaine is nearly comparabale to bupivacaine in terms of potency and duration of action with better safety profile.[5,38] Ropivacaine is less lipophilic hence less chances of central nervous system and cardiovascular toxicity.[14,15,17] Various studies have shown that 0.375% and 0.5% ropivacaine could be used for local wound infiltration, with maximum dose being *3 mg/kg*.[13,14,17,39] So, we had used 0.375 % ropivacaine in wound infiltration for post-operative analgesia.

Wound infiltration with local anesthetics has short duration of action (*30 min* to *6 hr*) even with longer acting anesthetic ropivacaine.[14] Despite use of longer acting ropivacaine, there is always need for adjuvants to prolong duration of analgesia. With single shot wound infiltration, duration of analgesia is more limited as catheter may have certain disadvantages like dislodgement and infection.[31] Various additives had been used to local anesthetic infiltration to improve quality and duration of post-operative analgesia. Tramadol, fentanyl, morphine, sodium bicarbonate and dexmedetomidine are commonly used as additive to local anesthetics in wound infiltration.[40–42]

Various studies has shown that infiltration with opioids could potentiate analgesic action of local anesthetics in wound infiltration.[40,41] As an adjuvant, tramadol is gaining popularity in wound

infiltration besides systemic use for pain control. Tramadol is a synthetic opioid used as an adjuvant to local anesthetic in wound infiltration. It may exerts its analgesic effects through μ receptors and inhibition of monoaminergic transmitters. Various studies has demonstrated that tramadol might had anti-inflammatory and local anesthetic action on peripheral nerves.[43–46] Various studies has shown that tramadol in dose of *1.5–2 mg/kg* could be effective in wound infiltration for post-operative analgesia.[19,39,47,48] So, in our study, we had used tramadol in dose of *2 mg/kg* for infiltration in open cholecystectomy surgeries.

Wound infiltration volume may depend on length of surgical incision. Various studies have shown that volume used for wound infiltration for post-operative analgesia could range from *20 ml–40 ml* depending on nature of surgery.[5,12,13,17,32,39] So. we had used total volume of *22 ml* in open cholecystecomy wound infiltration for post-operative pain control.

In our study, we found that VAS scores were significantly higher in control group (Group C) compared to other groups. These findings were indicating that wound infiltration with local anesthetic drugs might reduced pain score by providing post-operative analgesia. Duration of pain relief of wound infiltration with ropivacaine was comparable to that reported by study of Baudry *et al.*[49] Axelle V *et al.* also demonstrated that wound infiltration with ropivacaine after breast cancer surgery had lower pain score compared to control group during immediate post-operative period.[12] Jing Xian *et al.* also revealed that wound infiltration with ropivacaine after open hepatectomy decresed VAS score compared to saline group. These findings correlated with our study.[3]

VAS scores were also higher in ropivacaine group compared to ropivacaine-tramodol group. These findings were indicative of efficacy of tramodol as an adjuvant to ropivacaine to reduce pain score in post-operative period. When adjuvants were added to ropivacaine in wound infiltartion, pain scores were decresed significantly. Shaman *et al.* also stated that ropivacaine plus dexmedetomidine in local wound infiltration had significantly low pain score compared to ropivacaine alone for cesarean section.[5] Demiraran *et al.* revealed in their study that wound infiltration with tramodol at cesarean section had lower VAS score compared to saline group.[48] Murat *et al.* also found that tramodol in wound infiltration had lower pain scores. These findings were in correlation with our study.[34]

Duration of analgesia as defined by time for first rescue analgesic was significantly shorter in control group compared to other groups. Time for first rescue analgesic was longest for ropivacaine-tramodol group among all three groups. Our study revealed that duration of post-operative analgesia was higher in ropivacaine-tramodol group compared to ropivacaine group and saline group. Ozyilmaz *et al.* revealed that in lumbar disk surgeries, time for first recsue analgesic was ealiest in saline group followed by levobupivacaine group and then tramodol group.[47] In contrast to our study, Anders *et al.* found that wound infiltration with ropivacaine with or without fentanyl had no effects on post-operative pain relief after breast surgery.[32] Mitra *et al.* demonstrated that wound infiltration with tramadol as adjuvant to ropivacaine for lumber discectomies had longer time for first rescue analgesic requirement. These findings were in accordance to our study.[39] So, local anesthetics in wound infiltration could prolong duration of post-operative analgesia. When adjuvants (tramodol in our study) were added to local anesthetics, duration of analgesia was significantly prolonged.

Number of rescue doses in first *24 hrs* was higher in saline group compared to other two groups. These findings were indicating that patients with wound infiltration with local anesthetics required less rescue analgesic and better pain control. Mohta *et al.* found that there was less requirement of rescue doses in local anesthetic infiltration compared to control group for tubercular spine surgery.[17] Lee *et al.* also revealed similar findings for single incision laproscopic colectomy.[10] In contrast to our study, Murat *et al.* revealed in their study of wound infiltration for cesarean delivery that there was no difference between saline group and tramadol group in terms of rescue dose requirement.[34]

Rescue dose requirement were also higher for ropivacaine group compared to ropivacaine-tramodol group. These was might be due to addition of opioids (tramodol in our study) to local anesthetic in wound infiltration could prolong duration of analgesia. Mitra *et al.* revealed that local wound infiltration with ropivacaine-tramadol had no difference in rescue dose requirement compared to ropivacaine group.[39] Khajavi *et al.* found that subcutaneous wound infiltration with tramodol after renal surgery had lower rescue analgesic requirement.[14]

In our study, incidences of PONV in first *24 hrs* were nearly similar in all three groups. There was no increase incidence of PONV in ropivacaine-tramodol group. Khajavi *et al.* revealed that

subcutaneous tramodol infiltration after renal surgery had no increase risk for PONV.[14] Kong *et al*. also revealed that ropivacaine wound infiltration reduced incidence of PONV.[50] These findings were in correlation with our study. There was no increased incidence of PONV in ropivacaine-tramodol group indicating better safety profile of tramodol.

In our study, highest patient satisfaction at *24 hrs* was seen with ropivacaine-tramodol group and lowest with control group. These might be due to better quality of pain control with prolonged analgesia in ropivacaine-tramodol group. These findings also suggested that wound infiltration could provided better post-operative analgesia as part of multimodal approach hence better patient satisfaction. Mohta *et al.* found that patient satisfaction was higher for wound infiltration with local anesthetics compared to control group for tubercular spine surgery.[17]

Limitations

Wound infiltration as a part of multimodal approach should be considered in term of opioid sparing analgesic method. There are certain limitations to our study. Firts of all, sample size selected in our study was small and results obtained could not be applied to general populations. Second, surgeries were done by different surgeons hence tissue handling and wound infiltration done by them might affect results of our study. Third, it would be better to take follow up for atleast *48 hrs* post-operatively for more accurate results. So, we could access post,operative pain in late post, operative period, duration of hospital stay and any complications if any.

Conclusion

Both, ropivacaine and ropivacaine plus tramodol, in wound infiltration were highly effective for post-operative analgesia in open cholycystectomy surgeries. Ropivacaine-tramodol combination might be preferred in wound infiltration because of prolong duration of analgesia, least rescue analgesic requirement and better patient satisfaction without increase incidences of PONV.

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Original Research Article

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Comparison of Local Infiltration with Modified Pectoralis Block for Post-operative Analgesia after Modified Radical Mastectomy: An Open Label Randomized Trial

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Abstract

Objectives: Owing to safety of Modified Pectoralis block and limited studies available our study will compare the analgesic efficacy of Modified Pectoralis block with the combination of local and pocket infiltration after MRM. Design Open label randomized trial. *Setting:* Indira Gandhi Medical College, Shimla, HP, India. Participants 60 ASA physical status I-II patients (aged 25-65 years), scheduled for elective MRM procedures were recruited for the study. Intervention Group I (PEC 30 patients) received ultrasound guided PEC block preoperatively and Group II (local infiltration 30 patients) received local anaesthetic infiltration at surgical incision and pocket infiltration postoperatively. Patients were induced with standard general anaesthesia and then after reversal and shifted to recovery room. Main Outcome and Measure Post-operative pain assessment was done using Visual Analogue Score at O hour (Time taken as patient is shifted to PACU), 30 min, 1, 2, 4, 6, 12 and 24 hours. *Results:* In the PACU, the mean for rescue analgesia required in group 1 was 30.07 (SD = 3.473) and in group 2 was 8.13 (SD = 1.196) and this was statistically significant. The difference in mean of VAS score in group 2 at 6 hrs was (3.00) and in group 1 was (1.73) and this score increased significantly in next hours. The mean of total analgesic required in first 24 hrs in group1 was 0.00 (SD = 0.000) and in group 2 was 2.63 (SD = 556). *Conclusion:* Ultrasound guided PEC block had prolong post-operative analgesia as compare to local anaesthesia infilteration at surgical incision with pocket infilteration post-operatively.

Keywords: Anaesthesia; Analgesia; Pain; Post-operative; Mastectomy; PEC, Local anaesthesia infilteration.

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Introduction

Breast cancer is the most common cancer amongst women worldwide with an incidence rate that vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In India, the age standardized incidence rate of breast cancer varies from 9 to 32 per 100,000 women.[1] Patients after mastectomy and breast reconstruction suffer from acute nociceptive pain (36%) and chronic neuropathic pain syndromes (20–68%).[2] It is very important to manage the post-operative pain in patients undergoing modified radical mastectomy.[3] Appropriate post-operative analgesic technique after breast surgery is always

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dubious. Various practices like combination of both local and pocket infiltration, regional anesthetic and intravenous analgesic techniques have been used for the pain relief. Amongst the regional techniques thoracic epidural is considered as gold standard but is associated with the risk of neuraxial damage and persistent neurological deficits and also result in serious complications like intrathecal spread, epidural hematoma, and inadvertent intravascular injection.[4,5] Owing to the safety and greater pain relief by modified PEC block, it has become more familiar now-a-days among anesthetists compared to paravertebral and thoracic epidural nerve blocks for pain relief following breast surgeries.[6,7] However, so far, no data is available that compares modified PEC block with the combination of local and pocket infiltration. Therefore, we hypothesized that the PEC 2 block may effectively alleviate acute post-operative pain in patients undergoing MRM. The present study evaluated the analgesic efficacy of PEC 2 block in patients undergoing MRM. In addition, this study also compared the analgesic efficacy of Modified Pectoralis block with the combination of local anesthetic and pocket infiltration.

Materials and Methods

This study enrolled patients with breast cancer posted for modified radical mastectomy between *July 2016* and *May 2017*. After obtaining approval from our institutional scientific and research committee with registration number [ECR/533/INST/HP/2014] with ethical number G-5 (Ethic)/2015-10634, written informed consent was taken from 60 ASA physical status I-II patients (aged *25–65 years*), scheduled for elective MRM procedures. Exclusion criteria included history of any allergy to local anesthetic, bleeding disorder or receiving anticoagulant, BMI > *35 kg/m*^{2}, spine or chest wall deformity, pregnancy, prior breast surgery and patient declining to give consent. During preoperative visit, demographic data was recorded and visual analog scale score (VAS score:0–10,(0) No pain, (4–8) mild pain, (8–10) Worst pain) was explained to patients. Before surgery patients were randomly allocated according to the computer-generated sequence into two groups of 30 each. The group allocation numbers were concealed in sealed opaque envelopes that were opened after enrolment of the patients. All baseline and post-operative measurements were evaluated by an independent physician who was blinded to treatment allocation.

Group I (PEC 30 patients) received ultrasound guided PEC block pre-operatively and Group II (local infiltration 30 patients) received local anesthetic infiltration at surgical incision and pocket infiltration post-operatively. PEC block was performed with the patients in supine position, placing the ipsilateral upper limb in abduction position using a linear USG probe of high frequency (*6–13 MHz*, sonosite) with imaging depth of *4–6 cm* after sheathing. The USG probe was first placed at infraclavicular region after skin sterilization using chlorhexidine and moved laterally to locate the axillary artery and vein directly above first rib where pectoralis major and pectoralis minor muscles were identified with the help of USG probe. After infiltration of the skin at the puncture site with *3 ml* of lignocaine 2%, the 23 G needle was inserted in plane with USG probe to the facial plane between pectoralis major and pectoralis minor muscle and *10 ml* of levobupivaciane 0.25% was injected. Then USG probe was moved toward axilla till serratus anterior muscle was identified above 2nd, 3rd and 4th ribs and the needle was reinserted into the facial plane between pectoralis minor muscle and serratus anterior muscle and *20 ml* of 0.25% levobupicaine was injected in increments of *5 ml* after aspiration.

In Group II patients *10 ml* of 0.25% levobupivacaine was given as pocket infiltration and *20 ml* of 0.25% levobupivacaine was infiltrated at the incisional site by the surgeon before closure.

All patients received midazolam *1–2 mg* before induction of anesthesia and monitored with five leads ECG, pulse oximetry, non-invasive blood pressure and capnography. General anesthesia was induced with fentanyl *2 mg/kg*, propofol *1.5–2 mg/kg* and endotracheal intubation was facilitated with atracurium *0.5 mg/kg*. Anesthesia was maintained with isoflurane and O_2/NO_2 mixture with a fraction of 33% inspired oxygen. Fentanyl *1 mg/kg* in bolus doses was given intravenously if mean blood pressure or heart rate exceeded 20% of the pre-operative value. After recovery from anesthesia, patients shifted to post-anesthesia care unit for the first *2 hours*. Post-operative pain assessment was done using Visual Analog Score at rest at *0 hour* (Time taken as patient was shifted to PACU), *30 min*, *1,2,4,6,12* and *24 hours*. Post-operative rescue analgesia was given whenever the VAS score > 4 in the form of I.V. Diclofenac *75 mg* or I.V. Tramadol *100 mg* I.V. stat.

Nausea or vomiting lasting more than *10 minutes* was treated with ondansetron *0.1 mg/kg*. Patient satisfaction for post-operative analgesia was

recorded according to satisfaction score: Poor = 0; Fair = 1; Good = 2; Excellent = 3. Any untoward side effects or complications related to procedure and local anesthetic were recorded.

Statistical Analysis

All analysis was performed using IBM SPSS software version 22.0 (Statistical Packages for the Social Sciences, Chicago). The normally distributed data were compared by using Student's unpaired *t*-test, whereas non-parametric data were compared by chi-square test for intergroup differences. Intra-operative hemodynamic data were compared with baseline by repeated measures ANOVA followed by student's paired *t*–test. The pain scores, time to first rescue analgesia, and total *24 hr* analgesic consumption were compared by using Wilcoson W and Mann-Whitney *U*-test for pairwise comparisons. Confidence intervals were calculated for statistically significant differences. The sample size was calculated on the basis of a pilot study.

Results

This study enrolled patients with breast cancer posted for modified radical mastectomy between *July 2016* and *May 2017*. Before surgery patients were randomly allocated according to the computer-generated sequence into two groups of 30 each. The group allocation numbers were concealed in sealed opaque envelopes that were opened after enrolment of the patients. Group I (PEC 30 patients) received ultrasound guided PEC block pre-operatively and Group II (local infiltration 30 patients) received local anesthetic infiltration at surgical incision and pocket infiltration post-operatively.

The patient characteristic (age, body mass index and ASA) were comparable between the two groups (**Table 1**). The duration of surgery and anesthesia was comparable between the two groups.

Table 1: Patient Characteristics

Parameters	Group 1 (*n* - 30)	Group 2 (*n* - 30)	*p*
Age (*yrs*)	28.42 (mean)	32.58 (mean)	.354
Weigh t(*kgs*)	34.05 (mean)	26.95 (mean)	.114

n - Number of patients;

p - Statistically significance ($p < .05$).

In the PACU, the patients of Group 1 had significantly lower consumption of intravenous fentanyl as compare to Group 2 (**Table 2**). The mean time for first rescue analgesia in Group 1 was higher and statistically significant in Group 2. The mean for rescue analgesia required in Group 1 was *30.07 hrs* (SD = 3.473) and mean of first dose of rescue analgesia in Group 2 was *8.13 hrs* (SD = 1.196) and this was statistically significant (**Table 2**). VAS score was same for first *4 hrs* post-operatively in both the groups. The difference in VAS score became statistically significant between both the groups after *6 hrs* with mean of VAS score in Group 2 at *6 hrs* was (3.00) and mean of VAS score in Group 1 was (1.73) at *6 hrs* and this score increased significantly in next hours. VAS score was found to be statistically significant at 12, 18, 24, 30 and *60 hrs*. The mean of total analgesic required in first *24 hrs* in Group 1 was. 00 (SD = 000) and in Group 2 was 2.63 (SD = 556), (**Table 3**).

There was no significant difference between the groups with respect to HR, SpO_2, and mean arterial pressure during the peri-operative period. However, the intra-operative consumption of fentanyl was less in the PEC block group during MRM but not statistically significant.

No untoward effects like vascular injury, hemodynamic instability, pleural puncture or pneumothorax was seen and no case of allergic to local anesthetic was seen. No patient suffered with PONV in any of the group.

Table 2: Intra-operative and Post-operative data

Parameters	Group 1 (PEC)	Group 2 (LA)	Mann-Whitney U	Z	*p*
Total fentanyl at induction (*mg*)	109 (S.D.-7.348)	112 (S.D.-6.518)	343.5	-1.583	.114
Total fentanyl consumption intra-operatively (*mg*)	160.17 (S.D.-22.042)	168.00 (S.D.-9.777)	337.5	-1.672	.095
Time for 1st rescue analgesia (*hrs*)	30.07 (S.D.-3.473)	8.13 (S.D.-1.196)	.000	-6.696	.000
Total doses of rescue analgesia	.00 (S.D.-.000)	2.63 (S.D.-.556)	.000	-7.282	.000

p- statistically significance ($p < .05$).

Table 3: Comparison of VAS between two groups

	Group	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
VAS 0	LA infiltration	30	.07	.254	.046	.155
	PEC block	30	.00	.000	.000	.161
VAS 30	LA infiltration	30	.60	.498	.091	.003
	PEC block	30	.23	.430	.079	.003
VAS 60	LA infiltration	30	.87	.507	.093	.075
	PEC block	30	.63	.490	.089	.075
VAS 2	LA infiltration	30	1.43	.568	.104	.000
	PEC block	30	.97	.183	.033	.000
VAS 4	LA infiltration	30	2.07	.450	.082	.000
	PEC block	30	1.27	.521	.095	.000
VAS 6	LA infiltration	30	3.00	1.287	.235	.000
	PEC block	30	1.73	.450	.082	.000
VAS 8	LA infiltration	30	5.50	1.676	.306	.000
	PEC block	30	2.23	.971	.177	.000
VAS 12	LA infiltration	30	6.07	1.574	.287	.000
	PEC block	30	2.37	.850	.155	.000
VAS 18	LA infiltration	30	6.43	1.331	.243	.000
	PEC block	30	3.07	.740	.135	.000

Discussion

In this study, we have demonstrated that patients in Group 1 who received PEC block had better post-operative analgesia than patients who had received local anesthesia infiltration. The duration of analgesia was prolonged in Group 1 as assessed by the demand of first rescue analgesia by the patient. Also, the consumption of fentanyl in post-operative period was more in group of local anesthesia infiltration as compare to that of PEC block which was found to be statistically significant. Regional anesthetic techniques appear superior to intravenous analgesics with reduced post-operative pain, decreased post-operative nausea vomiting, respiratory depression and also cost saving.[9]

Various anesthetic techniques such as local wound infiltration, thoracic epidural, thoracic paravertebral and very recent fascial plane blocks have been used to provide analgesia after modified MRM.[10] Amongst the regional techniques thoracic epidural was considered as gold standard but was associated with the risk of neuraxial damage and persistent neurological deficits.[4] Previously many studies have supported the use of paravertebral block in breast surgeries, but it has increased risk of intravascular injection, bleeding, infection, nerve injury, short segment contralateral block and high failure rate as well. So, it might cause less complications than thoracic epidural but still more risky than ultrasound guided PEC 2 block.[11,12]

PEC block 1 was first performed in 2011, on 50 patients who had breast expanders placed as part of breast reconstructive surgery.[12] In 2012, another study compared PEC block 2 with the PEC block I introduced[14] Pectoral nerve block 1 (PEC 1) is given between pectoralis major and minor muscle, and modified pectoralis nerve block 2 (mPEC2) is performed between pectoralis minor and serratus anterior muscle along with PEC 1 block.[17] The advantage of this new modified technique of PEC block 2 was that it covered the axillary clearance in breast surgeries, maintaining good post-operative analgesia.[14] This is because PECs 2 block the pectoral, intercostobrachial, the intercostalis 3 and 6 and the thoracic nerves. The blockage of these all nerves help to provide complete analgesia.[7] Also, the spread of local anesthetic into the axilla has been demonstrated by dissection of cadavers and contrast distribution.[14,15] The pectoral nerve block was also found to be beneficial for axillary surgery.[16]

Furthermore, this technique was compared with paravertebral and thoracic epidural in breast surgeries and concluded that it was quite safe, with less incidence of pneumothorax than paravertebral block and lacking sympathetic nerve block as thoracic epidural.[12]

In 2014, the study was conducted on 60 patients; PEC block was compared with thoracic paravertebral block (second group) for post-operative analgesia. Patients receiving PEC block required decreased intra-operative fentanyl or

morphine consumption as well as had decreased incidence of post-operative nausea and vomiting.[6]

According to previous studies, no complications were associated with PEC 2 block.[3] Owing to safety of PEC 2 block, it has become more familiar among anesthetists now-a-days as compared to paravertebral and thoracic epidural nerve blocks with breast surgeries. A PEC 2 block is given when patient is in supine position and the needle is manipulated easily under ultrasound guidance. Also, the target areas of needle in PEC 2 block is distant from the pleura and epidural space.[3] Direct intravascular injection of local anesthetics is performed very rarely due to the lack of vaculature at the interfascial plane.[18,19] The more invasive techniques such as selective intercostal nerve blocks and thoracic paravertebral blockade may lead to pneumothorax or transient Horner's syndrome because of technique difficulty and dosage of drug used.[13]

In our study, the duration of post-operative analgesia was more in patients with PEC block than the patients who were given local anesthesia infiltration with pocket infiltration of local anesthetic. The total analgesic dose in the form of rescue analgesia required after PEC block was less than the total dose required by the local infiltration of local anesthetic. In general, local infiltration with pocket infiltration of wound is easy and safe but the limitation was the duration of post-operative analgesia and limited by the pharmacodynamics of the local anesthetic.

This study had several limitations. First, the PECS block was performed before the induction of general anesthesia which may have affected post-operative pain. Also, the wound dressing and a surgical crepe bandage dressing may have interfered with the response to sensory level test including post-operative pain. However, we speculated that the PEC 2 block was successfully performed based on the changes in mean blood pressure and heart rate during the incision. Consequently, this study did not present sensory test data. A second limitation was our inability to perform a double blind, placebo controlled study. However, the patients and investigators were blinded to group assignment, suggesting that the lack of ability to perform a placebo controlled study had little influence on study outcomes. One should also be aware that local anesthetic can spread along the fascial plane following PECS block can limit the use of electrocautery by the surgeon.[20]

This new PEC block is another step towards a new generation of ultrasound-guided nerve blocks. It is simple to perform *via* ultrasound guided and should potentially be associated with few side effects. Pending comparative randomized controlled clinical trials, the PEC block might prove to be an important clinical tool for the treatment of pain after thoracic and chest wall surgery.

Conclusion

Ultrasound-guided PEC block reduces post-operative pain scores, prolongs the duration of analgesia and decreases demands for rescue analgesics in the first *24 hours* of post-operative period compared to local anesthetic infiltration after modified radical mastectomy.

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Original Research Article

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Outcome of Oral Gabapentin in Total Abdominal Hysterectomies on Post-operative Epidural Analgesia

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Abstract

Background: Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies post-operative pain. *Objective:* To evaluate the role of gabapentin as pre-emptive analgesic in patients undergoing total abdominal hysterectomy. *Methods:* Aprospective, randomized clinical study was conducted and the patients were randomly allocated to two groups of 15 each with ASA Grade I and II. Patients in Group A were given oral gabapentin 1200 *mg 1 hour* before surgery whereas placebo was given to patients belonging to Group B. Epidural block is achieved in both groups with a bolus dose of 0.5% bupivacaine (maximum allowable dose–*2 mg/kg*) prior to surgery. After skin closure, the infusion dose is reduced to a lower concentration of Bupivacaine (0.0625%) at the rate of *2 ml/hr* and the patient will be shifted to HDU (high dependency unit). Data collected includes patients age, body weight, post-operative VAS scores, and tramadol *50 mg* I.V. doses given at *1, 4, 8, 12, 16, 20, 24 hours*. *Results:* Study revealed that the mean VAS score in the post-operative period is lower in group A (Gabapentin) as compared to group B (placebo). Mean number of total top ups with tramadol is lower in Group A (Gabapentin) as compared to Group B (Placebo). *Conclusion:* Pre-emptive use of gabapentin *1200 mg* orally significantly reduces the number of post-operative analgesic dose requirements and post-operative pain in patients undergoing total abdominal hysterectomy under epidural anesthesia.

Keywords: Gabapentin; Total abdominal hysterectomy; Pre-emptive analgesia.

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Introduction

Post-operative pain is typically regarded as a type of nociceptive pain involving peripheral mechanoreceptor stimulation, inflammatory, and neurogenic and visceral mechanisms, with a transient, reversible type of neuropathic pain[1] Gabapentin [1-(aminomethyl) cyclohexane acetic acid] is a structural analogue of gamma amino butyric acid (GABA), which was initially introduced in 1994 as an antiepileptic drug, particularly for partial seizures. It was soon found to be promising in treating neuropathic pain associated with post-herpetic neuralgia (PHN)[2,3], post-poliomyelitis neuropathy[4], and reflex sympathetic dystrophy[5].

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Placebo-controlled clinical trials also have indicated a role of gabapentin in treating pain related to diabetic neuropathy (DNP)[6] and PHN[7]. The concept of pre-emptive analgesia to reduce post-operative pain was founded on a series of successful animal experimental studies that showed central nervous system plasticity and sensitization after nociception.[8] Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of alteredcentral processing of afferent input, which amplifies post-operative pain.[9] Gabapentin has demonstrated analgesic effects in clinical trials as a pre-emptive analgesic and in acute post-operative pain management. So, the rationale behind the study to investigate whether pre-emptive use of gabapentin *1200 mg* orally could reduce post-operative pain and number of additional analgesics in the initial *24 hours* in patients undergoing total abdominal hysterectomy.

Materials and Methods

Study Design

A randomized control study involving 30 patients belonging to ASA 1 & 2, who were posted for elective total abdominal hysterectomies.

Study Setting

Tertiary care teaching hospital–major operation theatre, Department of Anesthesiology, Pushpagiri Institute of Medical Sciences, Thiruvalla, Kerala.

Sample Size

For a significant level of 5% and a power of 90%, and equal number in both groups,a pooled variance of 16; to find a difference of *6 hour* between the 2 Groups, the sample size required is 11. For accounting dropouts, the sample size is rounded to 15.

Study Population

30 female patients with American Society of Anesthesiologists (ASA) physical status 1 or 2 aged *35–60 years* scheduled for total abdominal hysterectomy.

Selection was based on inclusion and exclusion criteria:

Inclusion criteria

1. Age between *35–60 years.*
2. Physical status: American Society of Anesthesiologists (ASA) 1 or 2.

Exclusion criteria

(1) Patients with cerebrovascular disease, cardiovascular disease.

(2) Poorly controlled arterial hypertension.

(3) Coagulation defects.

(4) History of renal in-sufficiency.

(5) History of hepatic insufficiency.

(6) Hypersensitivity to the drug in study.

(7) Patients with baseline pulse < *60 bpm* and systolic BP < *100 mm Hg*.

(8) History of peptic ulcer.

Ethical Considerations

The study was conducted after attaining approval from research and ethical committee.

Informed Consent

Written informed consent was taken from all patients.

Methodology

Patient will be assigned to two groups of 15 each. Patients in Group A will be given oral gabapentin *1200 mg 1 hour* before surgery whereas placebo willbe given to patients belonging to Group B.

Pre-operative Evaluation

A thorough pre-anesthetic check-up was carried out. Detailed history was taken, airway and systems were examined. Pulse rate, blood pressure and bodyweight were noted. Routine investigations like hemogram, blood sugar, renal function test, liver function test, bleeding and clotting time, prothrombin time, international normalized ratio (INR), chest *X*-ray (PA) viewand electocardiogram were done and reviewed in all the subjects.

Pre-operative Preparation

All patients were kept fasting for *six hours* before surgery. All the subjects were pre-medicated with Tab. Ranitidine *150 mgTab*. Alprazolam *0.25 mg* on previous night and *two hours* prior to surgery.

Procedure

Epidural block was achieved in both group patients with a bolus dose of 0.5% bupivacaine (maximum allowable dose–*2 mg/kg*) prior to surgery. Intra-

operatively analgesia was maintained with 0.5% bupivacaine infusion at the rate of *4 ml/hr*. After skin closure, the infusion dose was reduced to a lower concentration of bupivacaine (0.0625%) at the rate of *2 ml/hr* and the patient was shifted to HDU (high dependency unit). VAS scores were assessed by an independent physician who was not aware of the group allocation on a scale of *0–10 cm* (0 mean no pain, 10 equals to worst imaginable pain) after *1, 4, 8, 12, 16, 20 and 24 hrs* after the surgery and at the same time patients were asked for any complication suffered by them. Whenever the VAS score was above 4 additional analgesia with *50 mg* tramadol I.V. was given. Total numbers of tramadol top ups received by each patient were also noted.

Data collection

Post-operative assessment of pain was done using VAS (visual analogue scale). Other parameters like, additional analgesic requirements, hemodynamic variables (HR) were also monitored at specific time intervals. All collected data were recorded in a tabular fashion on a printed study proforma that was prepared earlier.

Statistical methods

Data was analysed using computer software, statistical package for social sciences (SPSS). The categorical variableswere presented as percentages and frequencies. Continuous variables were expressed as means and standard deviations. Changes in variables were analyzedusing repeated measures ANOVA. Other outcome variables were tabulated and subjected to chi-square test. A *p* - value of less than 0.05 was considered statistically significant.

Results

Table 1: Age wise distribution of the study participants

Group	Sample	Mean	Standard deviation	*p* - value
Gabapentin	15	45.47	5.475	0.645
Control	15	46.40	5.501	

Mean age in Group A (Gabapentin) and Group B (Control) were *45.47 ± 5.475 years* and *46.40 ± 5.501 years* respectively. This difference in the ages between the two groups was statistically not significant (*p* - value = 0.645 > 0.05) (Table 1).

Table 2: Weight wise distribution of the study participants

Group	Sample	Mean	Standard deviation	p - value
Gabapentin	15	63.93	8.447	0.315 > 0.05
Control	15	66.93	7.583	

Mean weight in Group A (Gabapentin) and Group B (Control) were *63.93 ± 8.447 years* and *66.93 ± 7.583 years* respectively. This difference in the ages between the two groups was statistically not significant (*p* – value = 0.315 > 0.05) (Table 2).

The mean VAS score is lower in Group A (Gabapentin) as compared to Group B (Control) at *1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. Statistical analysis proved that there is significant difference in mean heart rate of the two groups at *1 hour, 4 hours,16 hours, 12 hours* after surgery (Table 3).

Comparison of baseline heart rate in the two groups indicates that there is no significant difference between the two groups. The mean heart rate is lower in Group A (Gabapentin) as compared to Group B (Control) at *1, 4, 12, 16, 20, 24 hours* after surgery. Statistical analysis proved that there is

Table 3: Distribution of VAS score in terms of hours after surgery

VAS Score (Hours after surgery)	Group	Mean	Standard deviation	*f* - value	*p* - value
1 hr	Gabapentin	0.67	0.724	147.875	0.000 < 0.05
	Control	4.13	0.834		
4 hr	Gabapentin	2.47	1.246	41.600	0.000 < 0.05
	Control	5.93	1.668		
8 hr	Gabapentin	4.80	1.568	0.257	0.616 > 0.05
	Control	4.53	1.302		
12 hr	Gabapentin	4.07	2.219	2.949	0.97 > 0.05
	Control	5.33	1.799		
16 hr	Gabapentin	3.47	0.315	4.9000	0.035 < 0.05
	Control	4.40	1.352		
20 hr	Gabapentin	4.13	0.915	12.785	0.001< 0.05
	Control	5.60	1.298		
24 hr	Gabapentin	4.07	1.223	0.980	0.331 > 0.05

significant difference in mean heart rate of the two groups at *4 hours, 12 hours, and 20 hours* after surgery (Table 4).

The mean MAP is lower in Group A (Gabapentin) as compared to Group B (Control) at 1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours after surgery. Statistical analysis proved that there is no significant difference in mean MAP of the two groups at various time periods (Table 5).

Comparison of baseline Sp02 in the two groups indicates that there is no significant difference between the two groups. The mean Spo2 is lower in Group A as compared to Group B at *1, 4, 8, 12, 16, 20, 24 hours* after surgery. Statistical analysis proved that there is no significant difference in mean saturation of the two groups at various time periods (p – value > 0.05) (Table 6).

Table 4: Comparison in the Heart Rate among the study groups

Heart rate	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	67.27	6.497	0.116	0.736 > 0.05
	Control	68.13	7.396		
1 hr after surgery	Gabapentin	72.93	11.548	0.085	0.773 > 0.05
	Control	74.20	12.307		
4 hrs after surgery	Gabapentin	75.33	9.926	8.970	0.006 < 0.05
	Control	84.13	5.566		
8 hrs after surgery	Gabapentin	83.20	13.007	3.181	0.085 > 0.05
	Control	74.33	14.196		
12 hrs after surgery	Gabapentin	77.00	9.554	4.234	0.049 < 0.05
	Control	84.07	9.254		
16 hrs after surgery	Gabapentin	74.47	8.766	0.005	0.946 > 0.05
	Control	74.73	12.372		
20 hrs after surgery	Gabapentin	75.67	12.760	7.766	0.009 < 0.05
	Control	87.07	9.392		
24 hrs after surgery	Gabapentin	75.53	8.903	0.489	0.490 > 0.05
	Control	78.53	14.030		

Table 5: Comparison in the Mean Arterial Pressure among the study groups

MAP	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	75.60	9.804	5.103	0.032 < 0.05
	Control	69.97	4.667		
1 hr after surgery	Gabapentin	76.87	10.439	0.020	0.88 > 0.05
	Control	77.53	14.952		
4 hrs after surgery	Gabapentin	78.13	14.530	8.104	0.008 < 0.05
	Control	92.67	13.409		
8 hrs after surgery	Gabapentin	87.07	15.691	1.461	0.237>0.05
	Control	81.07	11.113		
12 hrs after surgery	Gabapentin	80.13	10.862	3.840	0.060 > 0.05
	Control	87.80	10.564		
16 hrs after surgery	Gabapentin	79.47	12.682	0.005	0.943 > 0.05
	Control	79.80	12.497		
20 hrs after surgery	Gabapentin	82.33	16.800	1.952	0.173>0.05
	Control	89.47	10.426		
24 hrs after surgery	Gabapentin	78.20	12.214	1.235	0.276 > 0.05

Table 6: Comparison in the Spo2 among the study groups

Pulse oximeter	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	99.00	0.378	1.909	0.178
	Control	99.20	0.414		> 0.05
1 hr after surgery	Gabapentin	99.00	0.655	0.085	0.772 > 0.05
	Control	99.07	0.594		
4 hrs after surgery	Gabapentin	98.93	0.258	0.000	1.000 > 0.05
	Control	98.93	0.258		
8 hrs after surgery	Gabapentin	98.80	0.414	1.909	0.178 > 0.05
	Control	99.00	0.378		
12 hrs after surgery	Gabapentin	98.87	0.352	2.154	0.153 > 0.05
	Control	99.00	0.000		
16 hrs after surgery	Gabapentin	98.93	0.458	0.318	0.577 > 0.05
	Control	99.00	0.000		
20 hrs after surgery	Gabapentin	99.00	0.000	0.318	0.577 > 0.05
	Control	99.07	0.458		
24 hrs after surgery	Gabapentin	98.93	0.258	0.00	1.000 > 0.05
	Control	98.93	0.258		

Discussion

Gabapentin is a structural analogue of gamma-amino butyric acid. It has been first reported to be effective for the treatment of neuropathic pain and diabetic retinopathy. It has also been used successfully as a non- opoid analgesic adjuvant for post-operative pain management. It is effective in reducing narcotic usage post- operatively and is helpful in neuropathic pain due to cancer.

The mean VAS score is lower in Group A (Gabapentin) as compared to group B (Control) *at 1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. This was similar to the studies done by Turan *et al.*[10] and Anil verma *et al.*[11] However, VAS score in gabapentin group was higher than control group at the *8 hour*.

The mean heart rate is lower in Group A (Gabapentin) as compared to Group B (Control) at *1 hour, 4 hour, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. Statistical analysis proved that there is significant difference inmean heart rate of the two groups at *4 hour*,*12 hour*, and *20 hours* after surgery (p - value < 0.05). Turan, G *et al.*[10], found out in their study that oral gabapentin (*1.2 g* day) as an adjunct to epidural analgesia decreased pain and analgesic consumption. The VAS pain scores were significantly greater at *1, 4, 8, 12,* and *16 hr* after operation in patients receiving placebo than in those receiving gabapentin ($p < 0.001$). Compared with the placebo group, PCA requirements were significantly reduced in the gabapentin-treatment group at *24, 48*, and *72 hr* after surgery. In addition, oral analgesic consumption was less in the gabapentin-treated patients compared with the control group. Verma *et al.*[11] found out in their study that single oral dose of gabapentin given *2 hrs* before surgery provides better pain control as compared to the placebo and also reduces the requirement of epidural boluses in patients undergoing total abdominal hysterectomy without increase in frequency of side effects. Patients in the Group G (gabapentin) had significantly lower VAS scores at all times *2, 4, 8, 12* and *24 hrs* than those in the Group P (placebo). The total number epidural boluses demanded after surgery in the first *24 hr* in the Group G (gabapentin) (3.4 ± 1.6, mean ± SD) was significantly less than in the Group P (placebo) (5.6 ± 2.1, $p < 0.05$).[12,13]

Conclusion

Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies the post operative pain.[9] Many drugs have been proposed to attain the same. Our study found out that the mean VAS score in the post-operative period is lower in Group A (gabapentin) as compared to Group B (placebo). Hence, we conclude that a single oral dose of gabapentin given *1 hr* before surgery provides better pain control as compared to the placebo and also reduces the requirement of additional analgesics in patients undergoing total abdominal hysterectomies receiving epidural bupivacaine infusion.

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Safety and Success of Ultrasound Guided Interscalene and Cervical Plexus Block as a Sole Anesthesia Method for Acromioclavicular Joint Fixation: A Retrospective Observational Study

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Abstract

Purpose: The purpose of this study is to analyse the safety and success of combined interscalene-cervical plexus block as a sole anesthesia method for Acromioclavicular joint fixation retrospectively. *Methodology:* We retrospectively analysed and present a case series of acromioclavicular joint fixation surgery that were operated under combined interscalene-cervical plexus blockbetween *Jan 2017* and *Dec 2018* in our institute. Block success, any complications as inadvertent arterial puncture, hematoma formation, respiratory distress, Horner's syndrome, pneumothorax, and signs of local anesthetic toxicity from the records were evaluated. Any conversion to general anesthesia, intra-operative anesthetic supplementation and time to receive first dose of analgesics also analysed from the records. *Results:* After exclusion 32 patients were analysed and found 100% block success rate. None of them required conversion to general anesthesia. In our study, four patients developed hoarseness of voice (12.50%), and three patients complained of breathing difficulty (9.38%). No other major complications. *Conclusion:* The ultrasound guided combined interscalene and cervical plexus block able to provide a successful, safe and effective sole anesthesia technique for acromioclavicular reconstruction surgeries without major complications. Prospective comparative study would prove that it can be an alternate method over general anesthesia.

Keywords: Interscalene and cervical plexus block; Ultrasonographic guidance; Acromioclavicular joint fixation.

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Introduction

Acromioclavicular (AC) joint injuries are grouped according to the Rockwood classification system. Grades I and II injuries represent strain and partial tearing of supporting ligaments and are treated conservatively with excellent results. Surgical management is typically indicated for patients with Grades IV to VI Acromioclavicular joint injuries.[1] A large variety of stabilization methods have been introduced for the Acromioclavicular joint, including K-wire trans fixation, hook plates, arthroscopic tight rope, and suture anchors. One of the treatment modalities is Acromioclavicular joint reconstruction by open reduction and

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fixation using endo button tight rope. Surgical reconstruction of the dislocated Acromioclavicular joint requires exposure and instrumentation of the coracoid. A transverse incision is made over the Acromioclavicular joint for this surgery. Usually this surgery is done under general anesthesia, but after establishment of ultrasound guided interscalene and cervical plexus block, we can provide complete regional block with less failure rate.[2]

Aims

The purpose of this study is to analyse the safety and success of combined interscalene-cervical plexus block as a sole anesthesia method for Acromioclavicular joint fixation retrospectively. The primary objectives are to find the number cases converted to general anesthesia and number of cases required anesthetic supplementation during intra-operative period. The secondary objective is to analyse the occurrence of complications.

Materials and Methods

Following approval by our Institutional Research and ethical committee, the medical records of patients who underwent Acromioclavicular joint fixation surgery over two years (between *Jan 2017* and *Dec 2018*) were reviewed. Acromioclavicular joint fixation that were operated under combined interscalene and cervical plexus block using endobutton tight rope were included for study. Surgeries done under general anesthesia and Acromioclavicular joint stabilization done by other methods like hook plate, K-wire trans fixation and also by arthroscopic method were excluded resulting in a total of 32 patients.

Patients anesthetic records and drug charts were retrospectively reviewed starting from *Jan 2017* to *Dec 2018*. Also, available stored scanned images of the cases reviewed from the USG machine local storage system (Esaotemylab™Gamma, Italy). Demographic data of the patients age, sex, height, weight, ASA physical status, time of drug administration, type and volume of the local anesthetic used was noted. A standard institutional protocol followed in all patients planned for surgery under regional block. If patients planned for surgery under regional block, they were informed about technique of regional block. Routine informed consent was obtained and documented properly. Standard contraindications to interscalene nerve block included coagulopathy, local site infection, phrenic nerve paralysis, polytrauma with multiple fractures and hypersensitivity to local anesthetics (bupivacaine).

The technique used was ultrasound-guided 'in-plane' lateral to medial approach double-injection (first cervical plexus block followed by interscalene block) method. The patient was placed in a supine position with the head turned away from the side to be blocked. The skin was prepared using an antiseptic solution, and the transducer was dressed with a sterile cover. A *3–11 megahertz* linear transducer was used for performing the blocks. The related side of the patient was scanned by ultrasound in a transverse orientation across the neck with the probe marker facing medially. The blocks were performed using a 23 gauge (*38 mm* Dispovan) hypodermic needle. First superficial cervical plexus block was performed by placing the needle tip deep to the Sternocleidomastoid muscle along its tapering posterolateral border but superficial to the prevertebral fascia and *10 ml* of 0.375% bupivacaine injected. Followed by probe moved caudally to find out the cervical nerve roots at interscalene groove in short-axis view and *20 ml* of 0.375% bupivacaine was given. Distribution of the local anesthetic drug was visualized during the procedure. Standard monitors were applied and patients were sedated with inj. Midazolam (*0.03 mg/kg*), inj. Ondansetron (*4 mg*) and inj. Fentanyl (*1 mg/kg*). To know the desired effect, motor blockade was determined by loss of shoulder abduction and sensory blockade was assessed using the spirit cotton for cold sensation and pinprick test for pain at the surgery site compared with normal side before proceed to surgery. Blocks were performed by same anesthesia team experienced with ultrasound guided regional techniques and also procedure was done by the same surgery team.

A successful block was defined as one which did not necessitate the conversion to general anesthesia. Duration of surgery reviewed from anesthesia record and time to receive first dose of analgesic calculated by the difference in the time of administration of block and the time of first dose of analgesic received by the patient from patient post-operative nurse chart. Anesthetic records were analysed for rates of successful blocks, failed blocks necessitating conversion to GA and local or intravenous anesthetic supplementation. And also, complications such as seizures, hypotension, breathing difficulty, Horner's syndrome, pneumothorax and drug toxicity accompanying diseases of the patients were reviewed. Data were presented as mean ± standard deviation or percentages.

Results

We analysed medical records of 32 patients who underwent Acromioclavicular joint fixation surgery under ultrasound-guided interscalene and cervical plexus block over two years. Demographic data, clinical parameters and other parameters like ASA physical status and duration of surgery are shown in (**Tables 1 & 2)**. All patients were male, and most of them underwent surgery for right Acromioclavicular joint. In our study, we found 100% success rate and none of them required conversion to general anesthesia. In this study, no additional analgesics were used and no intravenous rescue analgesics was required intra-operatively except for one patient who received local anesthetic (*8 ml* of 1% lignocaine with adrenaline) infiltration due to extension of surgical incision involved T2 dermatomal area.

In our study, four patients developed hoarseness of voice (12.50%), and three patients complained of breathing difficulty (9.38%). They were monitored closely and their vital parameters and oxygen saturation were normal. Seven patients developed Horner's syndrome (21.88%), which is clinically insignificant. No treatment was required for those complications and subsides with recovery from block effect. In our study, intra-operative vitals were stable in all patients and there were no other major acute or chronic complications noted. The mean time to receive the first dose of analgesic observed in our study was *6.15 ± 0.52 hours*.

Table 1: Demograhic and intraoperative vitals data

Number of patients	**32**
ASA (I/II/III)	(21/8/3)
Parameter	Mean ± SD
Age (year)	38.78 ± 11.09
Weight (kg)	71.65 ± 6.72
Height (cm)	159.75 ± 7.22
Pulse Rate (Intra-operative)	81.22 ± 8.023
Systolic BP (Intra-operative)	128.12 ± 14.86
Diastolic BP (Intra-operative)	79.06 ± 8.39

†Mean ± standard deviation.

Table 2: Surgical and anesthesia outcomes

Duration of surgery (*minutes*)	61.03 ± 9.09†
Time duration to receive first dose of analgesia (*hour*)	6.15 ± 0.52†
Block success rate	100%
Additional anesthetic supplementation required	nil
Complications	
Horner's syndrome	21.88% (7/32)
Hoarseness of voice	12.50% (4/32)
Breathing difficulty	9.38% (3/32)

Discussion

In our study, we aim to report our clinical experiences of the ultrasound-guided combined interscalene cervical plexus block technique as a sole anesthesia method for open reduction and fixation of Acromioclavicular joint dislocation. Surgeries on clavicle and shoulder under ultrasound guided interscalene and cervical plexus block have been increasing now-a-days. Regional anesthesia is always better than general anesthesia but it has issues on safety and success rate.[3]

With the advent of ultrasound-guidance, interscalene brachial plexus block with superficial cervical plexus block has become ease and high success rate with less complications in view of phrenic nerve paralysis and intravascular injection leads to local anesthetic toxicity or other complications.[2–4] The possibility of phrenic nerve paralysis can be avoided by the local anesthetic drug spread limited to superficial cervical plexus area possible with direct imaging of needle location using ultrasound guidance.[5]

Although the incision for Acromioclavicular surgery is different from surgical incision for fracture clavicle, the incision is confined to the block area of interscalene and superficial cervical pexus, displays in (**Fig. 1**).

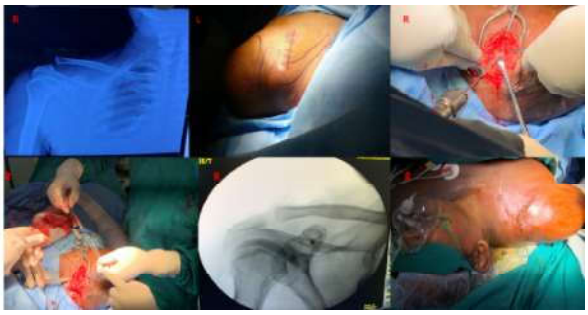

Fig. 1: Showing surgical incision area and procedures

In our study, we found 100% block success and no patients required conversion to general anesthesia. One patient received local anesthetic infiltration during intra-operative period. From the anesthesia record we found that, the patient was obese and required further surgical incision for better exposure below the lateral end of the clavicle anteriorly involves T2 dermatome. Around *8 ml* of 1% lignocaine with adrenaline was infiltrated from subcutaneous to surgical depth before extending incision below.

In our study, complications were minimal and did not receive any specific treatment. Four patients developed hoarseness of voice probably due to blockade of recurrent laryngeal nerve. And three

patients were presented with breathing difficulty which was mild subjective dyspnoea due to phrenic nerve dysfunction. Reassurance was given to these patients and they were explained that shortness of breath is mild subjective feeling and hoarseness of voice will resolve with recovery from block effect. All these complications were mild and managed with reassurance.

The combined interscalene-cervical plexus block for clavicular surgeries was used as a primary method of anesthesia by Balaban *et al.*[6], shown high success rate. They found this method effective for achieving surgical anesthesia and can be used as an alternate method to general anesthesia. Recent study by Banerjee *et al.*[7], compared general anesthesia with ultrasound-guided dual block (superficial cervical plexus block and interscalene brachial plexus block) for clavicular surgeries regarding various parameters such as intra-operative anesthesia, post-operative analgesia, and discharge time from post-operative care unit. The time interval for the first complaint of pain in interscalene brachial plexus block group is comparable with the time to receive the first dose of analgesic (*6.15 ± 0.52 hours*) in our study. When compare to Contractor *et al.*[8], our study shows, less incidences of side effects {Horner's syndrome (21.8%) and hoarseness of voice (12.5%)}. No other significant side effects were noted.

Limitations

Limitations of this study starts from its retrospective nature, and also several measurements like block performance, onset time, post-operative VAS score and analgesic requirement were not evaluated. Acromioclavicular joint reconstruction is a rarely performed intervention, a smaller number of cases was also a limitation. This should be a prospective study to analyse surgeon and patient satisfaction, post-operative pain score, analgesic duration, analgesic requirement and hospital stay in near future.

Conclusion

This retrospective analysis shows that ultrasound guided interscalene and cervical plexus block was safe with minimal complications and able to provide adequate surgical anesthesia. In conclusion, ultrasound guided combined interscalene and superficial cervical plexus block can be a sole anesthesia method of choice for Acromioclavicular reconstruction surgeries. Further prospective and comparative study would prove that it can be a safe and good alternative to general anesthesia.

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Evaluation of Transdermal Fentanyl for Post-operative Pain Relief

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Abstract

Background: Overview of post-operative pain control strategies lacks high quality effectiveness of the commonly used analgesics. Restricted use of strong systemic analgesics borne out of the fear of respiratory depression and other opoids related complications like nausea, vomiting, constipation, urinary retention etc. that results in failure to provide continuous analgesia of good quality in post-operative period. Therapeutic transdermal fentanyl (TTF) is a unique & innovative way of administering strong analgesic fentanyl transcutenously. Pharmacokinetic studies provides sufficient evidences that with TTF plateau analgesic concentration of fentanyl are attained after *8–12 hours* and are maintained over prolonged period of *72 hours* or more as the drug remains in circulation even after removal of patch. Therefore, TTF is expected to provide continuous analgesia of superior quality in post,operative period. *Materials and Methods:* 25 patients included in the study underwent major surgeries under uniform method of general anesthesia with gas, oxygen, relaxant and analgesic technique with controlled ventilation on Bain circuit. On these patients fentanyl transdermal patch releasing *50 mcg/hour* fentanyl was applied to the hair free skin on lateral chest wall and secured in place just before induction of anesthesia. We assessed the quality, duration and intensity of pain; patient's comfort score, requirements of rescue analgesics, efficacy & safety in its use, patient's satisfaction. We vigilantly observed them for any adverse cardiovascular, respiratory and local complications. *Results:* 68% (17/25) patients did not demand rescue analgesic dose during entire post-operative period and mean VAS score was less than 1 after *12 hours* post-operatively till the observation period of *72 hours*. Only 32% (8/25) of the patients required supplement analgesic with one/two dose of *75 mg* diclofenac sodium by intramuscular route. All patients expressed satisfaction with the analgesia provided; some had local complications like erythema at patch application site. The patients under study neither showed incidences of severe respiratory depression nor acute changes in cardiovascular parameter (HR, ECG and SBP, DBP) measurement throughout study period. The changes observed in cardiovascular and respiratory parameter were in-significant and did not require specific treatment. *Conclusion:* Therapeutic Transdermal Fentanyl releasing *50 mcg/hr* fentanyl can be safely used to control post-operative pain and is effective after *8–12 hours* of application with fewer side effects at patch application site.

Keywords: Postop Pain; Transdermal; Cardiovascular.

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Introduction

Traditionally systemic administration of narcotic analgesics (morphine/pethidine) remained cornerstone for management of post-operative pain for decades. This practice exposed patients to opioid related complications like disorientation, depression of respiration, urinary retention, bladder and bowel disturbances, nausea, vomiting, pruritus etc. Reluctance in their prescription is because of fear of addiction, caused incidences of break through pain in post-operative period. Frequent administration of analgesics on demand poses work load on nursing/paramedical staff.[1,2] Series of synthetic analogue of morphine were researched and several narcotic analgesics were marketed as safer alternatives. Fentanyl citrate is one such potent narcotic analgesic synthesized in 1960 by Paul Johnson and is favored in clinical anesthesiology because of its excellent pharmacological and pharmacokinetic profile and intra-operative cardiovascular stability. 1975 onwards fentanyl was widely accepted as intravenous supplement to produce balanced anesthesia.[3] Although, fentanyl can be used by traditional systemic route of administration but, its pharmacokinetic properties prompted investigators to explore alternative methods of its administration in an attempt to enhance the quality of analgesia. Fentanyl was used as continuous intravenous infusion, by intra and extra thecal route and also with peripheral nerve blocks. Newer modalities of its administration like patient controlled analgesia system (PCA) came into existence. Fentanyl proved its effectiveness in all the routes of its administration. But all these require technical expertise and are costly methods.[2,4,5] Patch is a medicated tape, typically consists of one or multiple layers of medicated membrane, or a drug reservoir or a semisolid matrix of drug; for application to the skin. Patch application provides constant rate of drug delivery non-invasively and maintains uniform concentration of drug in blood for several hours. Novel methods to improve diffusion of drug through intact skin incorporates chemical enhancers, ionophorasis, micro needle, ultrasound etc. with patch.[3,5] Therapeutic transdermal fentanyl patch (TTF) was initially available for management of chronic pain. Since 1999, TTF have also been used for management of acute moderate to severe post-operative pain. USFDA has approved use of iontophoresis patch after Phase III clinical trials for post-operative pain control. TTF is an advanced pain management system that addresses many concern of safety and convenience of use.[4] We are presenting our experiences of using transdermal fentanyl administration in management of post-operative pain following surgeries of moderate to severe category. Study was aimed to assess the safety, efficacy and quality of analgesia provided by TTF.

Aim of the present study to determine quality and duration of Post-operative pain control offered by transdermal administration of fentanyl and association of side effects with transdermal route as seen with systemic administration fentanyl.

Materials and Methods

The present study was conducted between *June 2013* to *February 2015* in R D Gardi Medical College Ujjain. We calculated the sample size assuming that with TTF, 30% patients would need additional analgesic and an alpha error of 0.05% and 80% power of study. We needed 21 patients for the study and therefore, the Clinical observations were made on 25 adult patients of both genders of ASA physical status I/II undergoing various surgeries under general anesthesia. Pre-operatively all the patients were screened to rule out presence of pre-existing cardiovascular, respiratory, renal or hepatic diseases besides routine biochemical and hematological tests. Patients were assured for providing additional analgesia on demand.

Patch Application

Fentanyl patch was applied immediately before induction of general anesthesia on right side of chest wall on non-hairy skin without using antiseptic or spirit and secured in place. Time of patch application was counted as zero hour. Anesthesia technique: Uniform technique of balanced anesthesia was adopted for all the patients. Induction of anesthesia was done with injection propofol *2–3 mg/Kg*, followed by succinyl choline chloride *2 mg/Kg* (max. dose *100 mg*) to facilitate endotracheal intubation. Maintenance of anesthesia was achieved with injection pentazocine *30 mg* and atracurium. Patients were ventilated with Gas, Oxygen (50:50) and Isoflurane 0.6% to 1.2%. The dose of Isoflurane was adjusted to keep pulse rate and blood pressure within ± 20% of pre-operative values. Continuous monitoring of vital signs was done using multi-parameter. Heart Rate, Electrocardiogram, SpO_2, non-invasive blood pressure recorded at *30 minutes* till recovery from anesthesia. Duration of surgery was recorded in minutes. Residual neuromuscular block was reversed with neostigmine *2.5 mg* with glycopyrrolate *0.4 mg*. Post-operative monitoring:

Upon arrival in recovery room vital parameters were recorded and initial pain assessment was done using VAS (Visual Analogue Scale). Patients having initial pain score more than 5 were given injection diclofenac sodium *75 mg* by intramuscular route. After recovery from general anesthesia and in no discomfort condition, patients were shifted to post-operative surgery ward and monitored for pain intensity, changes in vital parameters, respiratory rate, SpO_2, comfort score every two hours for *24 hours* and every *six hours* for next *24 hours* and every *12 hours* till *72 hours*. Patients having pain score more than 5 were administered a dose of diclofenac sodium *75 mg* by intramuscular route. Although the patch was removed after *48 hours* after application; Patients were kept under observation for *72 hours* for occurrence of delayed respiratory depression. Application site was inspected for local tissue reaction. Patients received oxygen through face mask @ *4 lit/mt*. till *12 hours* post-operatively. After *48 hours* patients were asked to comment on quality of pain relief as - satisfactory or not satisfactory.

Results

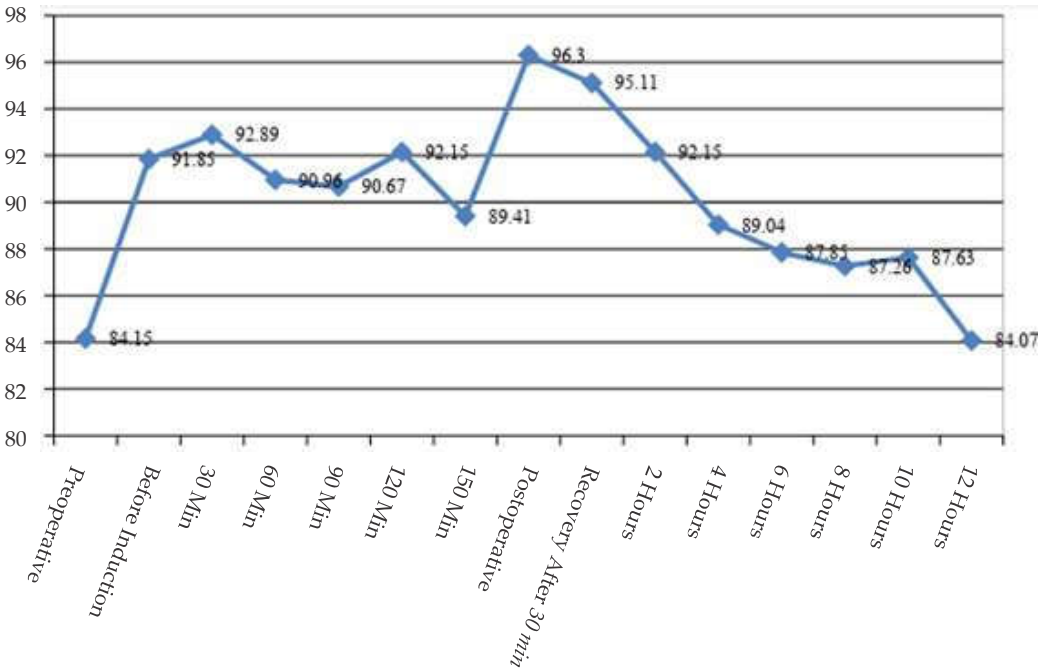
The demographic data of the patients, sex ratio and mean duration of surgery of patients under study shows in (**Table 1**).

The changes observed in mean Heart rate, systolic and diastolic pressure, ECG changes observed are displayed in (**Graphs 1–3**). After induction anesthesia and intubation an increase of *7.7 bpm* in HR, *5.41* and *5.0 mm* of *Hg* in systolic and diastolic pressure was observed. In remaining intra-operative period cardiovascular parameters remained within 20% of baseline value and did not needed treatment.

(Table 2) is showing the changes observed in mean heart rate, systolic and diastolic pressure

Table 1: Demographic details of Study Population

Parameter	Mean value	Range of observation
Age	*38.11 ± 11.69 years*	*20–60 years*
Height	*159.93 ± 9.58 cms*	*149–175 cms*
Weight	*60.56 ± 6.23 Kg*	*50–70 Kg*
Body Mass Index	24.00	
Male/Female	11:24	
Mean duration of surgery	*134.07 ± 27.49 minutes*	*100–200 minutes*



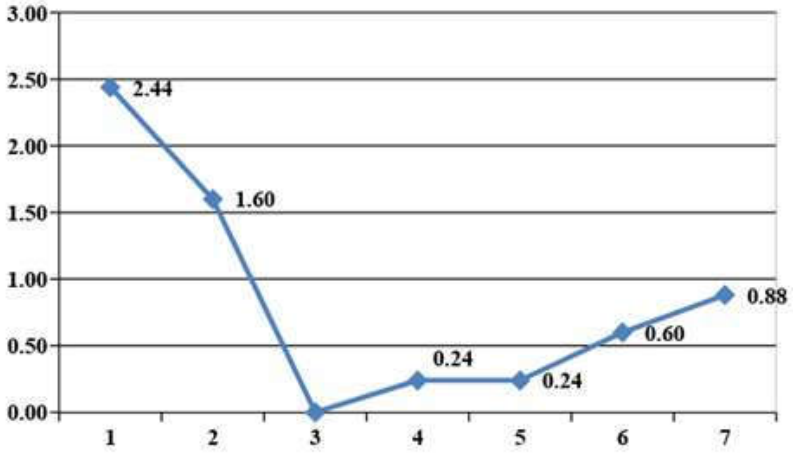
Graph 1: Mean Pulse rate in beats per minute

Table 2: Mean Heart rate, systolic and diastolic pressure during the first *12 hours* of TTF application

Time intervals	Mean value in *bpm* HR (Mean ± SD)	Mean value in *mmHg* SBP (Mean ± SD)	Mean value in *mmHg* DBP (Mean ± SD)
Post-operative on arrival in RR	96.30 ± 8.26	131.11 ± 13.28	86.07 ± 9.81
After 30 *min* in RR	95.11 ± 7.18	133.33 ± 8.66	87.93 ± 7.57
2 hours	92.15 ± 5.14	129.48 ± 8.22	81.56 ± 7.81
4 hours	89.04 ± 7.61	129.48 ± 8.69	82.89 ± 7.43
6 hours	87.85 ± 6.81	128.52 ± 10.12	82.96 ± 7.77
8 hours	87.26 ± 7.73	128.22 ± 9.30	81.56 ± 7.93
10 hours	87.63 ± 8.67	127.33 ± 10.05	80.81 ± 7.91
12 hours	84.07 ± 10.10	123.48 ± 11.38	77.33 ± 9.20

Table 3: Mean VAS score at different time intervals

Time intervals	VAS score mean value (Mean ± SD)
2 hours	2.37 ± 0.93
4 hours	1.89 ± 0.93
6 hours	1.96 ± 1.37
8 hours	2.00 ± 1.47
10 hours	1.63 ± 1.01
12 hours	1.67 ± 1.47
24 hours	0.00 ± 0.00
36 hours	0.24 ± 1.01
48 hours	0.24 ± 1.01
60 hours	0.60 ± 1.50
72 hours	0.88 ± 1.59



Graph 2: Mean comfort scale (post-operative to *72 hours*)

Table 4: Mean Pulse rate, systolic and diastolic blood pressure at post-op time intervals

Time intervals	Pulse rate in *bpm* (Mean ± SD)	Systolic blood pressure in *mmHg* (Mean ± SD)	Diastolic Blood Pressure in *mmHg* (Mean ± SD)
Post-operative (at *30 minutes* in RR)	96.72 ± 8.44	130.32 ± 13.42	85.52 ± 9.95
12 hour	84.16 ± 10.41	123.28 ± 11.76	77.04 ± 9.51
24 hours	70.32 ± 5.91	109.04 ± 10.63	68.40 ± 7.02
36 hours	71.44 ± 7.67	115.92 ± 11.28	74.00 ± 7.23
48 hours	72.32 ± 8.36	115.20 ± 9.95	73.12 ± 8.41
60 hours	77.60 ± 7.21	123.76 ± 10.45	78.24 ± 8.29
72 hours	77.68 ± 8.16	123.20 ± 9.35	78.56 ± 8.42

Table 5: Mean Value of comfort score at different time intervals

Time intervals	Mean value of comfort score (Mean ± SD)
2 hours	2.26 ± 0.53
4 hours	2.04 ± 0.44
6 hours	2.26 ± 0.71
8 hours	2.26 ± 0.66
10 hours	2.04 ± 0.44
12 hours	1.96 ± 0.71
24 hours	1.00 ± 0.00
36 hours	1.56 ± 0.65
48 hours	1.68 ± 0.63
60 hours	2.08 ± 0.40
72 hours	2.12 ± 0.33

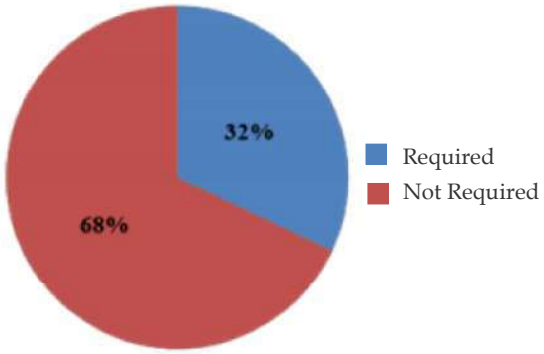
during the first *12 hours* of TTF application. We observed statistically and clinically insignificant fall in Heart rate, systolic and diastolic pressure. Patients were closely observed in remaining post-operative period upto *72 hours* and we observed insignificant changes in cardiovascular parameters did not found clinically significant changes. Mean value of oxygen saturation and respiratory rate were clinically and statistically insignificant. Patients were closely observed in remaining post-operative period up to *72 hours* and we observed in-significant changes in respiratory parameters did not found clinically significant changes. Patient was considered to have respiratory depression if RR was less than 10 and SpO_2 less than 90%. At *2 hours* of observation the mean VAS score was 2.37 ± 0.93. It decreased to *1.67 at 12 hours* post-operatively, indicating that some patients had mild post-operative pain after recovery from anesthesia. Patients who had VAS score equal to or more than 5 were given rescue analgesic dose by intramuscular route (injection diclofenac sodium *75 mg*). Patients were practically pain free between *12* and *72 hours*. **Table 3** shows the pain intensity measured on Visual Analogue Scale in early post-operative period (Pain Scale) (N = 25)

Table 4 shows that mean pulse rate, systolic and diastolic blood pressure remained close to pre and immediate post-operative mean and did not need corrective treatment. **Table 5** shows the mean comfort score majority of patients had a comfort score of 2–3 indicating that either patient had no pain or mild discomfort. Patient's comfort was monitored on 6 point scale used by Rafael and Miguel *et al.* (1995).

Table 6 shows the requirement of rescue analgesia *75 mg* diclofenac. Pain and analgesic requirement were lowest after *18–24 hours*. 68% (17/25) did not required where as only 32% patients demanded (14 doses) rescue dose of analgesic in majority in early post-operative period. In later period demand was reduced greatly.

Table 6: Requirement of rescue analgesia

Rescue analgesia	Number of patients and dose	% of patients
Required	8 (14)	32.0
Not required	17 (Zero)	68.0
Total	25	100.0



Graph 3: Requirement of rescue analgesia

Table 7 shows the patient's narration on quality of analgesia provided to them in post-operative period. All patients included in the study expressed satisfaction with the analgesia provided with or without need of rescue analgesia.

Table 7: Patient's satisfaction

Satisfied	25
Non-satisfied	00

Table 8 shows the complication rate of occurrence of side effect peculiar to systemic narcotic analgesic. No patient included in the study shown clinically significant fall in respiratory rate or oxygen saturation of hemoglobin requiring supplemental oxygen therapy after *12 hours* till the removal of patch at *48 hours* and thereafter till *72 hours*. No incidence of pruritus at the site of patch application or generalized itching was noted. 08 patients had erythema of surrounding skin of patch application site.

Table 8: Adverse drug reaction and local reaction to Patch

Parameter	Number of patients
Fall in respiratory rate	00
Low oxygen saturation (Less than 95%)	00
Urinary retention	00
Pruritus	00
Local erythema	08/25

Discussion

Pain management is an essential element of patient care and rehabilitation following surgery, as the results of clinical studies has shown that effective pain control can reduce patient's morbidity and associated healthcare cost in addition to minimization of patient's anxiety and physical discomfort.[6] Currently used Patient Controlled Analgesia (PCA) to treat post-operative pain introduces some potentially dangerous risk from invasive method, errors in manual programming of pump, needle related injuries, infection, limitation of mobility and high maintenance cost and availability for all patients.[6] Transdermal fentanyl is an advanced pain management system and addresses many concerns (issues) of safety and convenience of use. Transdermal Drug Delivery System (TDDS) needs more clinical evaluation across population divided according to body weight, age and time of surgery to evaluate potential impact of transdermal fentanyl[16] in clinical practice.

Dose Selection

Choice of transdermal delivery system of fentanyl with predicted delivery rate of *50 mcg/hr* was based on previous studies characterizing the relationship between serum concentration and analgesic effect in post-operative patients. We used matrix type of patch in the study.

Hug CC *et al.* (1984)[7] found that use of lower dose releasing fentanyl patch *25 mcg/hr* resulted in in-significant reduction in morphine consumption. Higher doses of *75 mcg/hr* placed the patients at risk of respiratory depression. IJ Broome *et al.* (1995)[8] have shown that peak analgesic concentration of *1.425 ng/ml* much below the dose (*3–4 ng/ml*) causing severe respiratory depression is achieved at *36 hours*. Higher rates of fentanyl delivery were associated lower VAS score and reduced morphine consumption as rescue analgesic. Concentration of fentanyl in plasma can be increased by administering intravenous loading dose at the start of surgery. Analgesic concentrations are maintained from *12 hours* to *48 hours*. Samy A *et al.* (2012)[9] found that reservoir and matrix type of patch are bioequivalent and delivered fentanyl at constant rate and shown liner kinetics. Authors found that using TDDS with predicted nominal rate *50 mcg/hr* achieve effective and safe analgesia in patients undergoing pelvi-abdominal cancer surgery. Severino *et al.* (1997)[10] questioned the utility of transdermal fentanyl in combination with intravenous morphine supplement considering multi factorial genesis of post-operative pain.

Time of Patch Application

We applied the fentanyl patch just before induction of anesthesia which did not take pharmacokinetic consideration of transdermal administration. Patients therefore, were expected to have plasma concentration lower than analgesic concentration in the window period and may demand rescue analgesic. For the above reasons in present study, we did not find adequate analgesia in all patients in first *12 hours* of patch application; 32% patients required rescue analgesia in immediate post-operative period. Similar to our findings Rawbotham *et al.* (1989),[11] Sevarino et al (1997),[12] Caplan *et al.* (1989),[13] Gourlay *et al.* (1990),[14] Alan N sandler *et al.* (1994),[15] did not consider pharmacokinetics and administered transdermal fentanyl before induction of anesthesia and reported in their studies that analgesic effect was commonly less apparent during first *12 hours* after application.

Pharmacokinetic profile suggests (IJ Broome *et al*. 1995)[8] that patch should be applied *8–12 hours* before anesthesia to achieve analgesia in early post-operative period. Those studies in which fentanyl patch applied *8–12 hours* before anesthesia provided adequate analgesia in early post-operative period.

Rescue Analgesia

In present study, *75 mg* of diclofenac sodium was administered by intramuscular route as rescue analgesic. We considered that post-operative pain is a complex phenomenon and involves multiple factors. Presence of inflammation in post-operative patients at the operative site is an important accompanying factor and hence, diclofenac was used.

In none of study, available anti-inflammatory drug was used as rescue analgesic. All reported studies employed morphine as supplemental analgesic either as bolos or PCA pump delivering pre-fixed dose of fentanyl intravenously.

Efficacy of Transdermal Fentanyl

Sixty-eight percent of the patients did not require additional rescue analgesic dose. Only 8 patients needed 14 doses of additional analgesia in majority in early post-operative period. Hug CC (1984)[7] reported that there is a interpersonal variability in serum concentration resulting from pharmacokinetic, pharmacodynamic and psychological factors. Sandler *et al.* (1994)[15] compared transdermal fentanyl in two different delivery rate

50 mcg/hr and *75 mcg/hr* with placebo for post-operative analgesia after abdominal hysterectomy. The patch was applied *two hours* before surgery and removed after *72 hours*. They found that there were significant reduction in pain intensity and rescue analgesic with delivery rate of *75 mcg/hr* when compared with placebo and there was significant reduction in rescue analgesic consumption with *50 mcg/hr* dose. Kilbride M *et al.* (1994)[16] reported a significant reduction in post-operative analgesic requirements after hemorroidectomy using *50 mcg/hr* fentanyl releasing patch. Severino *et al.* (1992)[10] compared two different delivery rate *25* and *50 mcg/hr* with placebo for post-operative analgesia after abdominal gynecological surgery. There were no differences in the pain intensity in both TDF group and no difference in rescue analgesia in TDF group with delivery rate of *25 mcg/hr* when compared with placebo group. There was only a significant reduction in the rescue analgesia in the TDF group with a delivery rate of *50 mcg/hr*.

Quality of analgesia

During entire observation period 68% patient felt no pain during entire observation period; Only in 8/25 patients experienced pain of intensity more than 5 on VAS in majority in early post-operative period for that 14 doses if rescue analgesic diclofenac sodium by intramuscular route were administered. Additional dose of diclofenac sodium reduced VAS at next observation.

Hug CC (1984)[7] reported that there is a interpersonal variability in serum concentration resulting from phramcokinetic and pharmacodinamic and psychological factors. And we decided to use diclofenac as multimodal approach. VAS score was 0–2 in all patients, after *12 hours* of patch application and was maintained till *48 hours* and started rising after wards. All patients expressed satisfaction with the analgesia provided with either transdermal fentanyl alone or with intramuscular diclofenac as rescue analgesia when they rated their pain intensity equal to or more than 5 and remained pain free throughout observation period. The safety and efficacy of transdermal fentanyl used as main post-operative analgesic in patients undergoing dorsal or lumbar spine fusion VAS score and rescue analgesic were lower in transdermal fentanyl group.

I power (2007)[6] reported that patients rated pain relief as good to excellent analgesia in post-operative period in ITF group in II and III *24 hour* period. Rafael M *et al.* (1995)[17] reported on patient's global satisfaction of analgesia in TDF groups in comparison to placebo. Difference between the two fentanyl group was not significant. Also reported that patient's comfort score significantly better compared with placebo group patients. We did not find significant lowering of pulse rate, blood pressure and ECG abnormality during post-operative observation period of *48 hours*. Cardiovascular parameters remained within ± 20% of their base line values. Similar to findings of our study Lauretti GR *et al.* (2009),[18] reported that all physiological parameters fluctuated within normal range. Philip WH *et al.* (1999)[19] in a review article shown that fentanyl at a plasma concentration of *3–4 ng/ml* alters carbon dioxide response of central respiratory control by 50%. These concentrations are not achieved with *50 mcg/ml* patch but cautions for continuous measurement of ventilation is preferable. Factors responsible for respiratory depression are type of surgical procedure, elderly patients, interaction with other central depressive drugs and individual variation in pharmacokinetics and pharmacodynamics.

Adverse drug reactions

The patients were observed for opioids like side effects after patch application. We did not notice significant fall in respiratory rate, fall in oxygen saturation below 95% requiring oxygen therapy, urinary retention and pruritus. Local complication like erythema occured at the patch application site in 32% cases which did not required any kind of treatment and resolved in *72 hours*. In contradiction to our findings Rafael M (1995)[17] reported that pruritus occurred in 10 patients who received *90–100 mcg/hr* than in patients and in 6 with *70–80 mcg/hr* group. Erythema was more common in *90–100 mcg* group. Possible reason for not confirming to our findings is employment of higher dose of transdermal fentanyl.

Conclusion

Transdermal fentanyl is superior, safe and effective method of managing post-operative pain over the traditional systemic opioid and can be a part of multimodal approach. It is free from side effects of intravenous administration. *50 mcg/hr* fentanyl releasing patch proved as safe and effective in patients of normal built.

Caution

It is important to observe patients for respiratory parameters closely for occurrence of respiratory

depression and oxygen supplement should be done as and when required. Medication (Injection Nalaxone) readily reverses the respiratory depression.

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Evaluation in Supraclavicular Brachial Plexus Block between Dexmedetomidine and dexamethasone as an Adjuvant to Local Anesthetic: A Double-Blind Prospective Study

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Abstract

Background: Supraclavicular brachial plexus block is a commonly employed regional nerve block technique for upper extremity surgery. Various adjuvants were added tolocal anesthetics in brachial plexus block to achieve rapid onset and prolonged block. *Objective:* To compare dexamethasone and dexmedetomidine as an adjuvant to local anesthetic agent in supraclavicular brachial plexus block with respect to onset and duration of sensory and motor block. *Methods:* Forty ASA I and II patients scheduled for elective upper limb surgeries under supraclavicular brachial plexus block were divided into two equal groups in a double-blinded fashion. Group one was given 0.25% Bupivacaine 2 milligram/kg aslocal anesthetic and Dexmedetomidine 1 microgram/kg as adjuvant. Group two was given 0.25% Bupivacaine 2 milligram/kg and Dexamethasone 100 microgram/kg as adjuvant. Onset and duration of sensory and motor blockade and hemodynamic stability were recorded. All patients were observed for any side effects and complications. All data were recorded, and statistical analysis was done. *Results:* Sensory block and motor block onset was earlier in dexmedetomidine group. The duration of blockade was also prolonged in dexmedetomidine group when compared with dexamethasone group and is not associated with any major side-effect. *Conclusion:* Dexmedetomidine is a better adjuvant than dexamethasone in supraclavicular brachial plexus block.

Keywords: Dexmedetomidine; Dexamethasone; Bupivacaine; Supraclavicular brachialplexus block.

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Introduction

Brachial plexus block is a popular and widely employed regional nerve blocktechnique for perioperative anesthesia and analgesia for surgery of the upper extremity. Various approaches have been described such as supraclavicular, interscalene, transscalene, infraclavicular and axillary. Supraclavicular approach is the easiest and most consistent method for surgery below the shoulder joint. Regional nerve block minimizes the stress response and using minimal anesthetic drugs is always beneficial for the patients with various cardio- respiratory comorbidities.[1] Local anesthetics alone for Supraclavicular brachial plexus block

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providegood operative conditions but have shorter duration of post-operative analgesia. Bupivacaine is used frequently for supraclavicular nerve block as it has long duration of action from *3* to *6 hr*. So, various adjuvant like opioids, clonidine, neostigmine, midazolam, dexamethasone etc. were added to local anesthetics in brachial plexus block to achieve quick, dense and prolonged block, but the results are either in conclusive or associated with side effects.[2] Dexmedetomidine is highly specific to α-2 adrenoceptors, yielding an α-2/α-1 ratio of 1620 6. In humans, dexmedetomidine has shown to prolong the duration of block and post-operative analgesia when added to local anesthetic in various regional blocks.[3–6] Dexmedetomidine when added to bupivacaine for supraclavicular brachial plexus block shortens the onset times for sensory and motor blocks and prolongs their duration. The significantly prolonged duration of analgesia obviates the need for any additional analgesics.[7] Addition of *8 mg* dexamethasone to bupivacaine 0.25% solution in supraclavicular brachial plexus block prolongs the duration of sensory and motor blockade, reduces the requirement of rescue analgesic in post-operative period.[8] So, the rationale behind the study was to test the hypothesis that dexmedetomidine when added as an adjuvant to local anesthetic in supraclavicular brachial plexus block enhanced the duration of sensory and motor block, duration of analgesia and quality of block as compared with dexamethasone.

Materials and Methods

Study design

A double-blind prospective study.

Study setting

Tertiary care teaching hospital-major operation theatre, Dept of Anesthesiology, Pushpagiri Institute of Medical Sciences, Tiruvalla, Kerala.

Study Population

40 patients of the age group *18–60 years* belonging to ASA Grade I and II who were posted for upper limb orthopedic surgeries under supraclavicular brachial plexus block. Selection was based on inclusion and exclusion criteria.

Sample size

With 80% power and 95% confidence, assuming equal number in both groups, to estimate a difference of *four hours* of sensory and motor blockade between dexmedetomidine and dexamethasone with pooled variants of 16, a sample size of 17 per group was estimated. For accounting drop outs the sample size is rounded to 20.

Inclusion criteria

1. Age between *18–60 years.*
2. Physical status American Society of Anesthesiologist (ASA) I and II.

Exclusion criteria

1. ASA grade more than two.
2. Known hypersensitivity to local anesthetic drugs.
3. Bleeding disorders.
4. Pregnant women.
5. Pre-existing peripheral neuropathy.
6. Patients already on dexamethasone or any adrenoceptor agonist/antagonist.

Ethical Considerations

The study was conducted after attaining approval from research and ethical committee of Pushpagiri Institute of Medical sciences, Tiruvalla.

Informed consen

Written informed consent was taken from all patients.

Methodology

Patients were assigned to two groups of 20 each as follows:

Goup 1: Dexmedetomidine group. Injection 0.25% Bupivacaine *2 milligram/kg* as local anesthetic an Dexmedetomidine *1 microgram/kg* as adjuvant.

Group 2: Dexamethasone group. Injection 0.25% Bupivacaine *2 milligram/kg* and Dexamethasone *100 microgram/kg* as adjuvant.

Pre-operative evaluation

A thorough pre-anesthetic check-up was carried out. Detailed history was taken, airway and systems were examined. Pulse rate, blood pressure and body weight were noted.

Pre-operative preparation

All patients were kept fasting for *eight hours* before

surgery. All the subjects were premedicated with Tab. Ranitidine *150 mg* Tab. Alprazolam *0.25 mg* on previous night and *two hours* prior to surgery.

Procedure

After allowing the patients to settle down in the operative room for a period of *five minutes*, baseline parameters like heart rate, blood pressure, and oxygen saturation were measured and recorded. All the patients were given brachial plexus through supraclavicular approach by an experienced anesthesiologist different from one assessing the patient intra and post-operatively. Each patient was made to lie supine, arms at the side, head turned slightly to the opposite side. The supraclavicular area was a septically prepared and draped. The tip of the index finger placed in the supraclavicular fossa directly over the subclavian artery pulsation which is used as the landmark. The pulsation can be felt in a plane just medial to the midpoint of the clavicle. After a skin wheal with local anesthetic approximately *1 cm* above the midclavicular point, the stimuplex needle is introduced through the skin and directed just above and posterior to the subclavian pulse and advanced slowly in caudal, medial and posterior directions. The nerve stimulator is initially set at 1.0 to 1.2 Ma. The needle is advanced until flexion of fingers is noted. If contraction is still observed with the nerve stimulator voltage decreased to *0.5 mA*, the local anesthetic solution is injected after confirming negative aspiration of blood. Onset and duration of sensory and motor blockade and hemodynamic stability were measured and recorded at specified time intervals. Sensory block was assessed by the pin prick method. Assessment of sensory block was done in the dermatomal areas at specified time intervals after completion of drug injection. Sensory onset was considered when there was a dull sensation topin prick.

Sensory block was Graded as:

Grade 0: Sharp pin felt.

Grade 1: Analgesia, dull sensation felt.

Grade 2: Anesthesia, no sensation felt.

Assessment of motor block was carried out by the same anesthesiologist at specified time intervals till complete motor blockade after drug injection. Onset of motor blockade was considered when there was Grade 1 motor blockade. Motor blockade was determined according to a modified Bromage scale for upper extremities on a 3-point scale:

Grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers.

Grade 1: Decreased motor strength with ability to move the fingers only.

Grade 2: Complete motor block with inability to move the fingers.

The duration of sensory block was defined as the time interval between complete injection of local anesthetic and when the patient first experienced pain in the post-operative period. The duration of motor block was defined as the time interval between complete administration of local anesthetic and complete recovery of motor function. All patients were observed for any side effects and complications.

Statistical Analysis

Collected data were compiled, entered and subjected to statistical analysis using Statistical Package for Social Sciences (SPSS) Version 20. For all statistical evaluation, an independent sample *t*-test was applied with probability value of < 0.05 was considered significant.

Results

Table 1: Age wise distribution of study participants

Group	Sample	Mean	Standard Deviation	P value
Dexmedetomidine	20	41.20	14.443	0.22>0.05
Dexamethasone	20	36.00	11.938	

As per shows in (**Table 1**) Mean age in Group 1 (Dexmedetomidine) and Group 2 (Dexamethasone) were *41.20 ± 14.443 years* and *36.00 ± 11.938 years* respectively. This difference in the ages between the two Groups was statistic indicates that the two Groups are more or less homogenous with respect to age and are hence comparable.

Table 2: Gender wise distribution of the study participants

Group	Percentage	
	Male	Female
Dexmedetomidine	65	35
Dexamethasone	50	50

There is no significant difference (p – value = 0.337 > 0.05) between Group 1 (Dexmedetomidine) and Group 2 (Dexamethasone) with respect to gender of the patients included in the study. This indicates that the two Groups are more or less homogenous with respect to gender andare hence comparable.

Onset of sensory block was earliest in Group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone) (p – value = 0.024 < 0.05). though the mean values of Group 1 is higher than Group 2.

Onset of motor block was earliest in Group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone) (p - value = 0.006 < 0.01).

Mean duration of sensory block was higher in Group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone) (p – value = 0.003 < 0.01). Mean values are higher in Group 1 as compared to Group 2.

Mean duration of motor block was higher in group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone (p – value = 0.018 < 0.05).

Comparison of baseline Heart rate in the two groups indicates that there is no significant difference between the two Groups. The mean heart rate is lower in Group 1 (Dexmedetomidine) as compared to Group 2 (Dexamethasone) at *zero minute*, *five minutes*, *ten minutes*, *twenty minutes*, *forty minutes*, *sixty minutes*, *eighty minutes*, *hundred minutes* and *one hundred* and. Statistical analysis proved that there is significant difference in mean heart rate of the two Groups at various time periods (p – value < 0.05).

Table 3: Onset of sensory block

Group	Sample	Mean	Standard Deviation	T value (with degrees of freedom)	P value
Dexmedetomidine	20	11.40	3.575	2.343 (38)	0.024<0.05
Dexamethasone	20	14.45	4.594		

Table 4: Onset of motor block

Group	Sample	Mean	Standard Deviation	T value (with degrees of freedom)	P value
Dexmedetomidine	20	15.57	4.475	2.918 (38)	0.006<0.01
Dexamethasone	20	20.25	5.159		

Table 5: Duration of Sensory Block

Group	Sample	Mean	Standard Deviation	T value (with degrees of freedom)	P value
Dexmedetomidine	20	1005.10	201.814	3.206 (38)	0.003<0.01
Dexamethasone	20	823.75	152.530		

Table 6: Duration of Motor Block

Group	Sample	Mean	Standard Deviation	T value (with degrees of freedom)	P value
Dexmedetomidine	20	983.10	196.756	2.465 (38)	0.018<0.05
Dexamethasone	20	833.25	187.633		

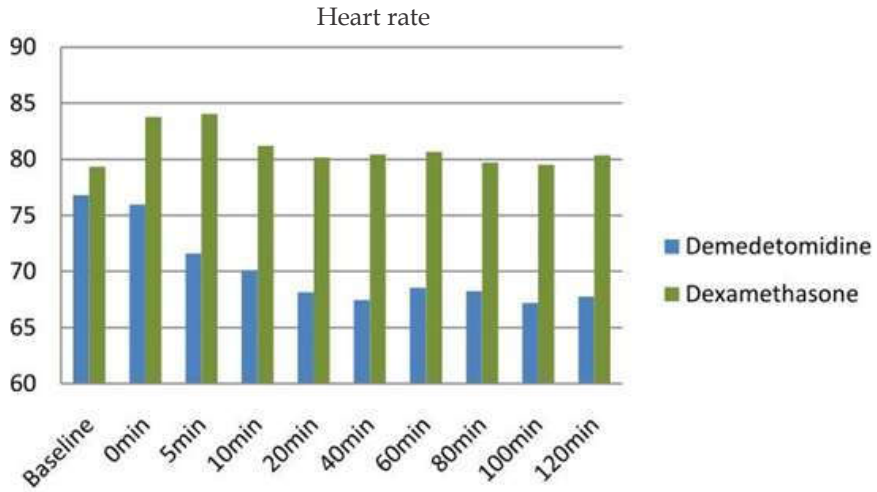

Fig. 1: Comparison of Heart rate among two groups

Discussion

The brachial plexus block for upper limb surgery has proved to be a safer and effective method of regional anesthesia. But it is a common observation that surgeries on upper limb are still being performed mainly under general anesthesia despite unanimous consensus toward regional anesthesia, due to one or the other reasons.Various approaches have been described such as supraclavicular, interscalene, trans scalene, infraclavicular and axillary, but they all are associated with some technical difficulties, in-adequate blocks and significant complications. The rate of conversion or supplementation with general anesthesia from brachial block is quite high. The supraclavicular block of the brachial plexus has many advantages over other approaches to brachial plexus block 33, 34, 35. It has the reputation of providing most complete and reliable anesthesia for upper limb surgery. It is performed at the trunk level where the plexus is presented most compactly.

Our study revealed that mean ages in Group 1 (Dexmedetomidine) and Group 2 (Dexamethasone) were *41.20 ± 14.443 years* and *36.00 ± 11.938 years* respectively. This difference in the ages between the two Groups was statistically not significant (p – value = 0.22 > 0.05).

In our study, there were 13 male patient and 7 female patients in Group 1 (Dexmedetomidine) and 10 male and 10 female patients in Group 2 (Dexamethasone). Our study revealed that there is no significant difference (p – value = 0.337 > 0.05) between Group 1 (Dexmedetomidine) and Group 2 (Dexamethasone) with respect to gender of the patients included in the study.

In our study, mean of onset of sensory block in Group 1 (Dexmedetomidine)is *11.40 ± 3.575 minute* and in Group 2 (Dexamethasone) is *14.45 ± 4.594 minute*. Onset of sensory block was earliest in group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone) (p - Value = 0.024 < 0.05).

In our study, mean duration of motor block in Group 1 (Dexmedetomidine) is *983.10 ± 196.756 minute* and in Group 2 (Dexamethasone) *833.25 ± 187.633 minute*. Mean duration of motor block was higher in Group 1 (Dexmedetomidine) and this was statistically significant when compared to Group 2 (Dexamethasone) (p – value = 0.018 < 0.05).

Our study revealed that with use of dexmedetomidine there was a mean heart rate change from baseline of *76.80 ± 11.985 beats per minute to 75.95 ± 11.578 beats per minute* at zero minute. Mean heart rate at *five minutes*, *ten minutes*, *twenty minutes*, *forty minutes*, *sixty minutes*, *eighty minutes*, *hundred minutes* and *one hundred* and *twenty minutes* were *71.6 ± 11.413*, *70.10 ± 10.290*, *68.15 ± 10.277*, *67.45 ± 10.149*, *68.55 ±11.180*, *68.25 ± 11.088*, *67.20 ± 10.670*, *67.75 ± 10.467 beats/minute* respectively. With use of dexamethasone there was a mean heart rate change from baseline of *79.35 ± 13.967 beats per minute* to *83.75 ± 14.825 beats per minute* at zerominute. Comparison of baseline heart rate in the two Groups indicates that there is no significant difference between the two Groups. The mean heart rate is lower in Group 1 (Dexmedetomidine) as compared to Group 2 (Dexamethasone) at *zero minute, five minutes*, *ten minutes*, *twenty minutes*, *forty minutes*, *sixty minutes*, *eighty minutes*, *hundred minutes* and *one hundred* and twenty minutes. Statistical analysis proved that there is significant difference in mean heart rate of the two groups at various time periods (p - value < 0.05).

Swami *et al.* in 2012 concluded that dexmedetomidine (*1 μg/kg*) when added to local anesthetic (bupivacaine 0.25%) in supraclavicular brachial plexus blocken hanced the duration of sensory and motor block and also the duration of analgesia.[9] Zhang *et al.* in 2014 also reported prolonged sensory and motor blockade duration patients who received dexmedetomidine.[10] Agarwal, *et al.* concluded, that dexmedetomidine when added to bupivacaine for supraclavicular brachial plexus block shortens the onset times for sensory and motor blocks and prolongs their duration. The significantly prolonged duration of analgesia the need for any additional analgesics. The added advantage of conscious sedation, hemodynamic stability, and minimal side effects makes it a adjuvant for nerve blocks.[7] Kathuria, *et al.* In 2015 concluded that in supraclavicular brachial plexus block addition of dexmedetomidine as adjuvant shortens the sensory and motor block onset time, prolongs both sensory and motor block duration. It also significantly delays the first demand for analgesia supplementation, decreases *24 hr* analgesic consumption and is not associated with any major side-effect. The action of dexmedetomidine is most probably peripheral than centrally mediated.[11]

Gandhi *et al.* reported that dexmedetomidine has better hemodynamic stability and greater post-operative analgesia.[12] Shrestha *et al.* reported that dexamethasone when added as adjuvant tomixture

of local anesthetics resulted in significantly early onset and longer duration of analgesia.[13]

Conflict of Interest: None declared

Source of Funding: None

Conclusion

We conclude that in supraclavicular brachial plexus block addition of dexmedetomidine as adjuvant to 0.25% bupivacaine shortens the sensory and motor block onset time, prolongs both sensory and motor block duration and is not associated with any major side-effect. The added advantage of conscious sedation and hemodynamic stability makes it a potential adjuvant for nerve blocks. Thus, it can be concluded that dexmedetomidine is a better adjuvant than dexamethasone in supraclavicular brachial plexus block.

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Corporate (collective) author

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